

Title: A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Multiple Rising Doses of MLN9708 for the Treatment of Subjects With ISN/RPS Class III or IV Lupus Nephritis

NCT Number: NCT02176486

Protocol Approve Date: 30 November 2017

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.



PHASE 1 PROTOCOL AMENDMENT

A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Multiple Rising Doses of MLN9708 for the Treatment of Subjects With ISN/RPS Class III or IV Lupus Nephritis

MLN9708_101 MRD Study in Lupus Nephritis

Sponsor: Takeda Development Center Americas, Inc.

One Takeda Parkway Deerfield, IL 60015

Takeda Development Centre Europe Ltd.

61 Aldwych

London WC2B 4AE, UK

Study Number: MLN9708_101

IND Number: 119,025 **EudraCT Number:** 2014-000125-21

Compound: Ixazomib (MLN9708)

Date: 30 November 2017 Amendment Number: 11

Date	Amendment Number	Amendment Type	Region
18 December 2013	Initial Protocol	Not applicable	Global
28 April 2014	1	Substantial	Global
26 August 2014	2	Substantial	United Kingdom
06 February 2015	3	Substantial	Global
16 March 2015	04	Substantial	United Kingdom
08 June 2015	05	Substantial	Global
01 July 2015	06	Substantial	United Kingdom
07 August 2015	07	Substantial	Global
08 August 2015	08	Substantial	United Kingdom
24 May 2016	09	Substantial	Global
23 June 2016	10	Substantial	United Kingdom
30 November 2017	11	Substantial	Global

CONFIDENTIAL PROPERTY OF TAKEDA

This document is a confidential communication of Takeda. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Takeda except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the study.

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided.

Issue	US Contact	Europe Contact
Serious adverse event and pregnancy reporting	Personal Protected Data	
Medical Monitor (medical advice on protocol, compound, and medical management of subjects) Responsible Medical Officer (carries overall responsibility for the conduct of the study)		

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Personal Protected Data	

1.3 Protocol Amendment 11 Summary of Changes

This document describes the changes in reference to the protocol incorporating Amendment No. 11. Through feedback from investigators, the Sponsor has determined the need to refine the study's eligibility criteria to be more reflective of the current clinical practice without affecting the objective integrity of the study. In addition, this amendment adds an Open-Label Treatment Extension Period to allow subjects to receive up to 3 additional cycles of open-label ixazomib treatment at the discretion of the investigator.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

Full details on changes of text are given in Appendix K.

Changes in Amendment 11

- 1. Updated the drug metabolism and concomitant medication information to reflect recent population pharmacokinetic (PK) analyses and drug-drug interaction study results from an ixazomib study (Study C16009) demonstrating that cytochrome P-450 inhibitors do not affect ixazomib PK and clarified details about PK assessments.
- 2. Added optional Open-Label Treatment Extension Period to the Study Design to allow treatment with up to 3 additional cycles of ixazomib at the discretion of the investigator.
- 3. Updated the safety summary conclusion with latest safety data from the Investigator's Brochure
- 4. Revised Inclusion Criterion 5 to allow subjects who have proteinuria ≥1 g/day due to a recent lupus nephritis (LN) flare, and who are refractory to current standard of care for those subjects who do not have a kidney biopsy within 2 years of the Screening.
- 5. Revised Inclusion Criterion 6 to allow subjects with Class V or Class V with Class II nephritis and urine protein creatinine ratio levels of ≥1 into the study rather than current criteria of >3.
- 6. Revised Inclusion Criterion 11 to allow subjects who received ≤2.0 mg ixazomib in earlier cohorts, rather than <2 mg ixazomib, to be re-enrolled into Cohorts B and C (2.0 mg and 3.0 mg).
- 7. Revised Exclusion Criterion 10 to add a stipulation to IgG <75% of lower limit of normal to allow subjects with IgG >4.2 g/dL into the study if the cause of low IgG is due to LN proteinuria and all other causes of hypo-gammaglobulinemia have been ruled out.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

at a same a	
Signature of Investigator	Date
	_
Investigator Name (print or type)	
T	-
Investigator's Title	
Location of Equility (City, State)	-
Location of Facility (City, State)	
Location of Facility (Country)	-

TABLE OF CONTENTS

1.0	ADMINISTRATIVE INFORMATION	2
1.	Contacts	2
1.2	2 Approval	3
1.3	Protocol Amendment 11 Summary of Changes	4
2.0	STUDY SUMMARY	12
3.0	STUDY REFERENCE INFORMATION	20
3.	Study-Related Responsibilities	20
3.2	Principal Investigator	20
3.3	3 List of Abbreviations	21
3.4	4 Corporate Identification	23
4.0	INTRODUCTION	24
4.	Background	24
	4.1.1 Systemic Lupus Erythematosus	24
	4.1.2 Lupus Nephritis	24
	4.1.3 Proteasome Inhibition in SLE and LN	25
	4.1.4 Proteasome Inhibitor Ixazomib.	26
	4.1.4.1 Nonclinical Toxicology	26
	4.1.4.2 Drug Metabolism and PK	28
	4.1.4.3 Clinical Experience	29
4.2	Rationale for the Proposed Study	34
5.0	STUDY OBJECTIVES AND ENDPOINTS	35
5.1	Objectives	35
	5.1.1 Primary Objective(s)	35
	5.1.2 Secondary Objectives	35
5.2	2 Endpoints	35
	5.2.1 Primary Endpoints	35
	5.2.2 Secondary Endpoints	35
	5.2.3 Exploratory Endpoints	36
	5.2.4 Additional Safety Endpoints	37
6.0	STUDY DESIGN AND DESCRIPTION	38
6.	5 8	
6.2	2 Justification for Study Design, Dose and Endpoints	43
6.3	Premature Termination or Suspension of Study or Investigational Site	46
	6.3.1 Criteria for Premature Termination or Suspension of the Study	46

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites	46
6.3.3 Procedures for Premature Termination or Suspension of the Study or the	
Participation of Investigational Site(s)	
7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS	47
7.1 Inclusion Criteria	47
7.2 Exclusion Criteria	49
7.3 Excluded and Restricted Medications, Procedures and Dietary Products	51
7.4 Diet, Fluid, and Activity Control	52
7.4.1 Criteria for Discontinuation or Withdrawal of a Subject	53
7.4.2 Dose Escalation Criteria	54
7.4.3 DLTs, Dose Modifications, and Stopping Rules	55
7.5 Procedures for Discontinuation or Withdrawal of a Subject	59
8.0 CLINICAL TRIAL MATERIAL MANAGEMENT	60
8.1 Study Medication and Materials	60
8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling	60
8.1.1.1 Investigational Drug	60
8.1.1.2 Concomitant Medications for Treatment of SLE While on Study	
Medication	
8.1.1.3 Corticosteroids Taper and Rescue Therapy	
8.1.2 Storage	
8.1.3 Dose and Regimen	
8.1.4 Overdose	
8.2 Study Medication Assignment and Dispensing Procedures	
8.3 Randomization Code Creation and Storage	
8.4 Investigational Drug Blind Maintenance	
8.5 Unblinding Procedure	
8.6 Accountability and Destruction of All Study Medication	
9.0 STUDY PLAN	
9.1 Study Procedures	
9.1.1 Informed Consent Procedure	
9.1.2 Pharmacogenomic Informed Consent Procedure	
9.1.3 Demographics, Medical History, and Medication History Procedure	68
9.1.4 Safety Assessments	
9.1.4.1 Tuberculosis Screening	
9.1.5 Physical Examination Procedure	69
9.1.6 Weight, Height, and Body Mass Index	69

9.1	.7 Vital	Sign Procedure	70
9.1	.8 Docu	mentation of Concomitant Medications	70
9.1	.9 Docu	mentation of Concurrent Medical Conditions	70
9.1	.10 Proce	dures for Clinical Laboratory Samples	70
9.1	.11 Contr	aception and Pregnancy Avoidance Procedure	73
9.1	.12 Pregn	ancy	74
9.1	.13 ECG	Procedure	74
9.1	.14 Addit	ional Assessments	75
	9.1.14.1	Urinalysis	75
	9.1.14.2	eGFR	75
	9.1.14.3	Definition of Complete and Partial Renal Responses	75
	9.1.14.4	Confidential Company Information	76
	9.1.14.5	FACT/GOG-NTX	77
9.1	.15 Pharn	nacodynamic Sample Collection	77
		nacogenomic and Other Sample Collection	
9.1		ample Collection	
	9.1.17.1	Collection of plasma and Company for PK Sampling for Ixazomib.	78
	9.1.17.2	Bioanalytical Methods Information	79
9.1	.18 PK Pa	arameters	79
	_	ration, Reconstitution, and Dispensation	
9.1	.20 Docu	mentation of Screen Failure	80
9.1	.21 Docu	mentation of Randomization	80
9.2	Monitorin	ng Subject Treatment Compliance	80
9.3	Schedule	of Observations and Procedures	80
9.3	.1 Scree	ning	80
	9.3.1.1 Sc	creening Visit	81
9.3	.2 Rando	omization	82
	9.3.2.1 D	ay 1 (Cycle 1, 2 and 3)	82
	9.3.2.2 D	ay 2 (Cycle 1)	84
	9.3.2.3 D	ay 8 (Cycle 1, 2 and 3)	84
	9.3.2.4 D	ay 15 (Cycle 1, 2 and 3)	84
		ay 16 (Cycle 3 only)	
		ay 22 (Cycle 1, 2 and 3)	
9.3	End o	f Treatment Visit/Early Termination/Final Visit	85
	9.3.3.1 D	ay 28 (Cycle 3)/Final Visit/ET/EOT	86

9.3.4 Open-I	Label Treatment Extension	87
9.3.5 Follow	y-up Visit	88
9.4 Blood Vol	ume	89
10.0 PRETREATM	MENT EVENTS AND ADVERSE EVENTS	91
10.1 Definitions	S	91
10.1.1 Pretrea	atment Events	91
10.1.2 AEs		91
10.1.3 Addition	onal Points to Consider for PTEs and AEs	91
10.1.4 SAEs		93
10.1.5 Manag	gement of Clinical AEs of Interest.	94
10.1.5.1	Diarrhea	94
10.1.5.2	Nausea and/or Vomiting	94
10.1.5.3	Volume Depletion	94
10.1.5.4	Renal AEs	94
10.1.5.5	Erythematous Rash With or Without Pruritus	95
10.1.5.6	Thrombocytopenia	95
10.1.5.7	Prophylaxis Against Risk of Infection	95
10.1.5.8	Peripheral Neuropathy	96
10.1.5.9	Hypoglobulinemia	96
10.1.6 Severit	ty of PTEs and AEs	96
10.1.7 Causal	ity of AEs	96
10.1.8 Relation	onship to Study Procedures	96
10.2 Procedures	S	97
10.2.1 Collect	tion and Reporting of AEs	97
10.2.1.1	PTE and AE Collection Period	97
10.2.1.2	PTE and AE Reporting	97
10.2.2 Collect	tion and Reporting of SAEs	98
10.2.3 Report	ing of Abnormal Liver Function Tests	98
10.3 Follow-up	of SAEs	98
11.0 STUDY-SPEC	CIFIC COMMITTEES	100
12.0 DATA HAND	LING AND RECORDKEEPING	101
12.1 Electronic	CRFs	101
12.2 Record Re	tention	101
13.0 STATISTICA	L METHODS	103
13.1 Statistical	and Analytical Plans	103

1	3.1.1 Analysis Sets.	103
1	3.1.2 Analysis of Demographics and Other Baseline Characteristics	103
	3.1.3 Medical History and Concurrent Medical Conditions	
	3.1.4 Medication History and Concomitant Medication	
	3.1.5 PK Analysis	
	3.1.6 Pharmacodynamic and Exploratory Analysis	
1	3.1.7 Safety Analysis	104
	13.1.7.1 AEs	104
	13.1.7.2 Kidney function Evaluation	105
	13.1.7.3 Clinical Laboratory Evaluation	105
	13.1.7.4 Vital Signs	105
	13.1.7.5 Electrocardiograms	105
13.2	Interim Analysis and Criteria for Early Termination	105
13.3	Determination of Sample Size	105
14.0	QUALITY CONTROL AND QUALITY ASSURANCE	106
14.1	Study-Site Monitoring Visits	106
14.2	Protocol Deviations	106
14.3	Quality Assurance Audits and Regulatory Agency Inspections	107
15.0 E	ETHICAL ASPECTS OF THE STUDY	108
15.1	IRB and/or IEC Approval	108
15.2	Subject Information, Informed Consent, and Subject Authorization	109
15.3	Subject Confidentiality	110
15.4	Publication, Disclosure, and Clinical Trial Registration Policy	110
1	5.4.1 Publication and Disclosure	110
1	5.4.2 Clinical Trial Registration.	111
1	5.4.3 Clinical Trial Results Disclosure	111
15.5	Insurance and Compensation for Injury	111
16.0 F	REFERENCES	112
LIST O	F IN-TEXT TABLES	
Table 4.	Study C16004 Most Common (>30% of Subjects in MTD Cohort) AEs Regardless of Causality by Dose Cohort	31
Table 4.1	b Summary of MLN9708 (ixazomib) Clinical Oncology Studies With Once Weekly Oral Dosing	32

Table 6.a	Summary of the Simulated Human Exposures Margins Relative to Nonclinical Toxicity Studies and Clinical MTD	45
Table 7.a	Prohibited Medications	52
Table 7.b	Dose Increase Factors	54
Table 7.c	Monitoring of Hematologic Toxicities and Dose Modification/Drug Stopping Rules	57
Table 7.d	Monitoring of Non-Hematologic Toxicities and Dose Modification/Drug Stopping Rules	58
Table 8.a	Treatment Groups	64
Table 9.a	Clinical Laboratory Tests	71
Table 9.b	Collection of Blood Samples for PK Analysis during the Double-Blind Treatment Period.	78
Table 9.c	Approximate Blood Volume	
Table 10.a	Takeda Medically Significant AE List	
Table 14.a	Windows for PK Sample Collection (Cycle 1 and Cycle 3)	
LIST OF INFigure 6.a Figure 6.b	-TEXT FIGURES Schematic of Study Design	
LIST OF AP		
Appendix A	Schedule of Study Procedures: Double-Blind Treatment Period	114
Appendix B	Responsibilities of the Investigator.	122
Appendix C	Elements of the Subject Informed Consent	124
Appendix D	Investigator Consent to Use of Personal Information.	127
Appendix E	Collection, Storage, and Shipment of Bioanalytical Samples	128
Appendix F	Total Blood Volume of Blood Withdrawal	132
Appendix G	Instructions for Processing and Shipping of Plasma Samples for Pharmacogenomics	134
Appendix H	Criteria for Classification of Systemic Lupus Erythematosus	136
Appendix I	Pathology Classification of LN	141
Appendix J	Diagnostic Criteria for Psychoactive Substance Dependence	143
Appendix K	Detailed Description of Amendments to Text	145

2.0 STUDY SUMMARY

Name of Sponsor(s):	Compound:	
Takeda Development Center Americas, Inc., Takeda Development Centre Europe Ltd. ixazomib (MLN9708)		
Title of Protocol: A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Multiple Rising Doses of MLN9708 for the Treatment of Subjects With ISN/RPS Class III or IV Lupus Nephritis		EudraCT No.: 2014- 000125-21
Study Number: MLN9708_101	Phase: 1b	

Study Design:

This study is a phase 1b, randomized, double-blind, placebo-controlled, safety, tolerability, and pharmacokinetic (PK) study of multiple-rising doses (MRD) of ixazomib for the treatment of subjects with International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Class III, IV or V changes [excluding Class III (C), IV-S (C), and IV-G (C)] or WHO 1982 classification of Class III, IV, or V (excluding Class IIIc and IVd) lupus nephritis (LN). It is anticipated that 4 ixazomib dose levels will be examined. At least 5 subjects (4:1) will be recruited into the 0.5 mg dose group (Cohort A), at least 5 subjects (4:1) in the 2.0 mg dose group (Cohort B), 8 subjects (6:2) in the 3.0 mg dose group (Cohort C), and 8 subjects (6:2) in the 4.0 mg dose group (Cohort D). Subjects will be considered eligible on the basis of study inclusion and exclusion criteria, verified by an adjudication committee, and randomized. Following each of the 0.5, 2.0, and 3.0 mg dose cohorts, available PK and safety data will be evaluated before escalation. For each dose level cohort, the Safety Review Committee (SRC) will carefully review the available safety, tolerability, and PK data to determine if dosing should be escalated in the next cohort, lowered, or expanded within the same dose cohort to obtain additional information before a dose-escalation decision, or stopped. After 5 subjects are recruited in the 4.0 mg dose group (Cohort D) and complete at least 1 cycle of ixazomib or placebo, an analysis may be conducted on available PK data and blinded safety data from all cohorts. Subject numbers may be increased as appropriate per cohort to a total number not to exceed 40 subjects in all cohorts combined. Two subjects with Class V or Class V with Class II nephritis are permitted per cohort. Subjects will be treated with three 28-day cycles of ixazomib or placebo. Subjects who successfully completed 12 weeks of doubleblind treatment without any AE resulting in dose modification or discontinuation of the study drug (defined in Section 7.4.3) will be eligible to receive up to 3 additional cycles of open-label ixazomib at the discretion of the investigator and confirmed by the Takeda medical monitor/designee following the end of the Double-Blind Treatment Period. The subjects need to begin the Open-Label Treatment Extension Period within 4 weeks of completing Cycle 3 of double-blind treatment.

Each 28-day cycle will consist of 3 once-weekly oral doses of 0.5, 2.0, 3.0, or 4.0 mg of ixazomib (dosage strength is stated as the active boronic acid ixazomib) or placebo, depending on the cohort. Subjects who received a dose \leq 2.0 mg and completed all cycles including the Follow-up Period, will be permitted to re-enroll into the 2.0 and 3.0 mg dose groups, provided they have no drug-related adverse events (AEs) >Grade 1 that required study drug dose modification, no AEs >Grade 2, continue to meet all inclusion and exclusion criteria, and the SRC (consisting of sponsor personnel and the coordinating investigator) have reviewed and approved re-enrollment. Subjects must be receiving standard of care treatment for LN and remain on their current stable and allowed therapies during the Screening Period and throughout the duration of the study (Section 8.1.1.2).

The study consists of the following Periods: a Screening Period (up to 35 days), a Double-Blind Treatment Period (Day 1 to Day 84) and either a Follow-up Period or an Open-Label Treatment Extension Period (Day 85 to Day 168). For those subjects who enter the Open-Label Treatment Extension Period, the last study visit will be 30 days after the last open-label treatment cycle or Day 168, whichever is longer. Subjects can be randomized 24 (+11) days after Screening (between Days -24 and -35) and once safety laboratory tests and inclusion/exclusion criteria have been reviewed and confirmed by the investigator. Diagnostic criteria, disease activity measures, and treatment history will be documented, and required laboratory investigations initiated. Subject eligibility will be reviewed by an adjudication committee. The responsibilities and criteria of this committee will be defined in an adjudication

charter.

Following verification of eligibility, subjects will return to the clinic on Day 1, undergo baseline assessments, laboratory testing, and will be randomized to either ixazomib or placebo within each cohort/dose level. The Double-Blind Treatment Period will consist of three 28-day treatment cycles (Cycles 1, 2, and 3) without intra-subject dose escalation. Subjects will receive ixazomib treatment on Days 1, 8, and 15 of each 28-day cycle. The second and third cycles will commence on the first day following Day 28 of the preceding cycle (ie, with a period of 13 days between the third drug administration of a cycle and the first drug administration of the following cycle). The Double-Blind Treatment Period will be limited to 3 complete cycles with ixazomib or placebo, over an expected duration of 12 weeks. However, the total treatment period may be longer than the standard 12 weeks if delays between cycles are necessary due to AEs. After completion of Cycle 3 of the Double-Blind Treatment Period, the subject will either enter the Follow-up Period or enter an optional Open-Label Treatment Extension Period at the investigator's discretion and confirmed by the Takeda physician/designee. The Follow-up Period or the Open-Label Treatment Extension Period (Day 84). The Open-Label Treatment Extension Period will be limited to up to 3 cycles of treatment with ixazomib on the same dose and schedule that subjects were receiving in the double blind period over an expected duration of 12 weeks.

Subjects will receive ixazomib cycles consisting of doses of 0.5 mg (Cohort A), 2 mg (Cohort B), 3 mg (Cohort C), or 4 mg (Cohort D), or placebo. The ascending dose cohorts will be enrolled sequentially. Dosing of subsequent cohorts will not commence until at least 5 subjects in Cohorts A and B and 8 subjects in Cohort C have received at least 1 dose of investigational drug and have reached Day 28 of Cycle 1 or have completed their last evaluation within Cycle 1 with a satisfactory review of all available safety and tolerability data. Subjects discontinued or withdrawn after randomization for nonsafety reasons will only be replaced if the number of subjects per cohort evaluable for safety on Day 28 of Cycle 1 is reduced below 6 subjects for Cohorts C and D, below 5 subjects for lower than 3.0 mg dose cohorts, or the SRC recommends expanding with the same dose to obtain additional information before a dose-escalation decision. Down-titration of ixazomib is permitted for individual subjects for safety and tolerability reasons at any time during the Treatment Period, except for subjects receiving 0.5 mg in Cohort A. If necessary for safety or tolerability reasons or in the judgment of the investigator, ixazomib treatment should be stopped altogether an End of Study Visit should be completed. The subject should then complete the remainder of the study period as the Follow-up Period. Dose modification and dose deferral should be discussed with the Sponsor's Medical Monitor; guidelines for the modification or deferral of doses will be provided. During the Double-Blind Treatment Period, ixazomib will always be dosed at the study site and subjects will return to the clinic for each administration of ixazomib. During the Open-Label Treatment Extension Period, subjects will receive the first dose of each cycle at the clinic and the other 2 weekly doses can be given to the subjects to take at home. All subjects will return to the clinic every 4 weeks to receive the first dose of each cycle. For scheduling flexibility, study visits can take place ± 2 days from each scheduled day during the Treatment Period and ± 1 week during the Follow-up Period. A minimum of 120 hours should occur between ixazomib doses. Any variance in the dosing schedule should not alter the schedule of subsequent dosing.

Subjects will undergo safety laboratory assessments, total immunoglobulin G, M, and A (IgG/IgM/IgA), LN assessments including but not limited to urine protein to creatinine ratio (UPCR), estimated glomerular filtration rate (eGFR), anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, and complement C3 and C4 levels via a central laboratory according to the schedule in Appendix A. Pharmacogenomic (PGx) and exploratory biomarker samples will also be sent to a central laboratory for analysis.

Ixazomib is an investigational, orally bioavailable 20S proteasome inhibitor with an estimated terminal elimination half-life ($t_{1/2}$) of ~ 4 to 9 days in plasma. For Cohorts A to D, plasma concentrations of ixazomib over time will be evaluated following the first dose of Cycle 1 and following the last dose of Cycle 3 of the Double-Blind Treatment Period. Predose samples will be collected before each dose in Cycles 1, 2, and 3 of the Double-Blind Treatment Period. Available PK data will be reviewed as part of the overall safety and tolerability evaluation of ixazomib in LN and for the dose escalation decision.

Recent evidence suggests that genetic variation accounts for differing responses to bortezomib therapy. A single nucleotide polymorphism (SNP) at position 11 in the PSMB1 gene (in the region encoding the leader sequence for

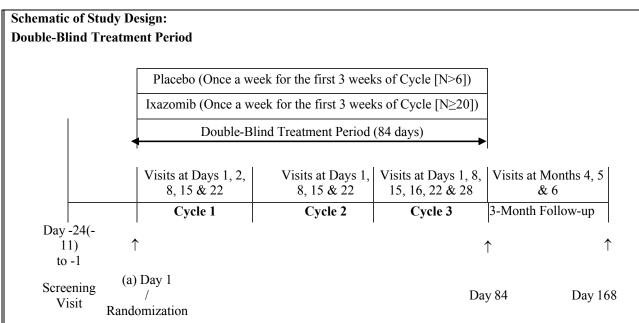
the beta subunit of the 20S proteasome) has been associated with reduced proteasome activity and is associated with enhanced bortezomib activity in multiple myeloma and relapsed follicular lymphoma. Company Confidential Information

In addition, hematology and chemistry safety laboratory assessments will be collected before each dose of ixazomib during the Double-Blind Treatment Period and before each cycle of open-label treatment; the results of all available laboratory tests will be reviewed by the investigator before administration of the scheduled dose of ixazomib. If the central laboratory results are not available for the Open-Label Treatment Extension Period an additional safety laboratory assessment can be conducted at the local laboratory before dosing and they will be recorded in the electronic case report forms (eCRFs). A negative urine pregnancy test result is required before each administration of investigational drug at the visits specified in the schedule of events table.

In common with other immunosuppressant agents, ixazomib may have additional effects on host defense. The subject's immunization status should be reviewed at the Screening Visit, and all appropriate vaccinations should be completed at least 1 month before treatment. These may include but are not limited to pneumococcal and inactivated influenza vaccines.

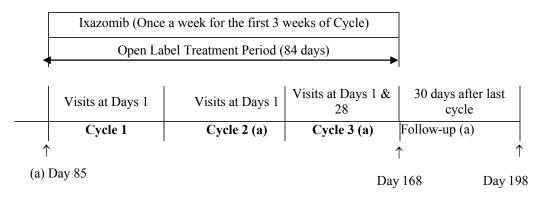
If lymphopenia is noted, subjects may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex viruses, and cytomegalovirus. Antiviral therapy such as acyclovir or valacyclovir may be initiated at the onset of infection after administration of ixazomib. Other antivirals are also acceptable. Provision of medication will be arranged by the investigator from local suppliers and will be reimbursed by the Sponsor.

Each investigator will review any safety findings and laboratory results to determine if a subject should receive the next dose within each cycle. For the Double-Blind Treatment Period, the investigator will evaluate safety and tolerability for each subject on Day -1 and before each dose during every cycle. On Day 22 of each cycle, the investigator-led team will evaluate all available safety information for the subject to determine eligibility to initiate the subsequent cycle. For the Open-Label Treatment Extension Period the investigator will evaluate safety and tolerability for each subject before each cycle as specified in the Table of Events. A schematic of the study design is presented below:



(a) At randomization, subjects will be assigned 0.5, 2.0, 3.0, or 4.0 mg of ixazomib or placebo, each 4-week cycle will consist of 3 once-a-week oral doses. In case abnormal, clinically significant findings are observed upon discharge, subjects may be brought back to the clinic for re-evaluation per investigator's discretion.

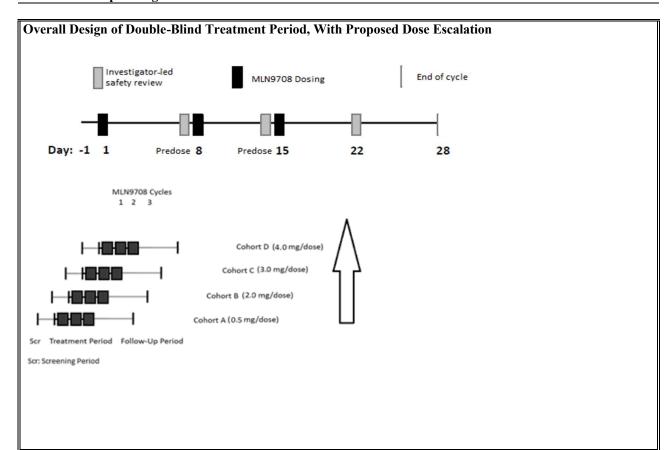
Open Label Treatment Period



(a) All subjects who enter the Open-Label Treatment Extension Period will have monthly visit up to at least Day 168. If open-label treatment is terminated before the completion of all 3 cycles, an end of treatment visit will be performed (Day 28 of current cycle) and the subsequent cycle Day 1 visits will be replaced with a follow-up visit.

Dose escalation will be sequential, with escalation only considered after all the following conditions have been met;

- 1. All subjects in the preceding cohort have been randomized;
- 2. All subjects of the preceding cohorts have received at least 1 dose of investigational drug and have reached Day 28 of Cycle 1 or have completed their last evaluation within Cycle 1.
- 3. Before any dose escalation, the SRC will review all the available safety, tolerability and PK data of the entire dose-level cohort to decide if dose escalation is appropriate.



Primary Objective:

To characterize the safety and tolerability of ixazomib when administered as multiple oral doses at escalating dose levels in subjects with LN.

Secondary Objectives:

- 1. To assess changes from Baseline in UPCR in LN subjects following multiple administrations of ixazomib.
- To evaluate the effect of ixazomib on kidney function, as assessed by changes from Baseline in serum creatinine and eGFR.
- 3. To evaluate the effect of ixazomib on antibody to double-stranded DNA (anti-dsDNA) antibodies titer and complement C3/C4 levels.
- 4. To characterize the PK of ixazomib in LN subjects when ixazomib is administered over 3 cycles consisting of 3 doses per cycle.

Subject Population: Male or female subjects aged 18 to 75 years inclusive, with ISN/RPS class III, IV or V LN, who have had inadequate response to at least 3 months of treatment with an immunosuppressive regimen including single or sequential use of either cyclophosphamide (CYC), mycophenolate mofetil (MMF), mycophenolic acid (MA) or azathioprine (AZA).

Number of Subjects:	Number of Sites:	
Estimated total: ≤40 subjects	Approximately 21 sites in the US and Europe (such as	
	UK, Germany, Spain, Russia and Ukraine)	

Dose Level(s):	Route of Administration:
active compound 0.5 mg or matching placebo	Oral
active compound 2 mg or matching placebo	
active compound 3 mg or matching placebo	
active compound 4 mg or matching placebo	
Each capsule contains ixazomib equivalent to the stated dose in mg of the active boronic acid ixazomib.	
Duration of Treatment:	Period of Evaluation:
Double-Blind Treatment Period:	~210 days including Screening period
Total of 3 cycles over approximately 84 days of duration. Each 28-day cycle consists of once weekly dosing for 3 weeks followed by 13 days without ixazomib or placebo	
Open-Label Treatment Extension Period:	
Up to a total of 3 cycles over approximately 84 days of duration. Each 28-day cycle consists of once weekly dosing for 3 weeks followed by 13 days without ixazomib	

Main Criteria for Inclusion:

Male or female subjects with ISN/RPS class III, IV, V or WHO classification of class III, IV, or V LN with coexisting classes permitted who have inadequate response to at least 3 months of treatment with an immunosuppressive regimen including single or sequential use of either CYC, MMF, MA or AZA; and non-pregnant, non-lactating female subjects who are 18 to 75 years of age inclusive, at the time of signing consent; capable of understanding and complying with protocol requirements; must be able to understand and sign a written informed consent. Subjects with a confirmed diagnosis of LN who have not had a renal biopsy within 2 years of screening and who cannot have a renal biopsy during the Screening Period may be eligible for the study if they have proteinuria of ≥1 g/24 hours due to a LN renal flare occurring within 1 year of the screening. A LN renal flare is defined as at least a doubling of proteinuria with no other explanation such as a secondary pathology (eg, diabetic nephropathy) or change in medication (eg, reduction of angiotensin-converting enzyme/angiotensin II receptor blocker).

Main Criteria for Exclusion:

Subjects having severe, active central nervous system lupus; (British Isles Lupus Assessment Group [BILAG] A or B); or an autoimmune disease other than SLE as their main diagnosis; or have drug-induced SLE.

Use of any excluded or prohibited medications or supplements outlined in the protocol.

Main Criteria for Evaluation and Analyses:

Safety:

Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), and TEAEs leading to withdrawal.

Changes in clinical laboratory values including chemistry, hematology. Changes in vital signs including body temperature, respiration, sitting and standing blood pressure, or heart rate.

Electrocardiogram (ECG) findings.

Subject-reported peripheral neuropathy (functional assessment of cancer therapy [FACT]/GOG-NTX version 4).

PK:

During the Double-Blind Treatment Period, blood samples (3 mL) will be collected for the determination of plasma concentrations of ixazomib Company Confidential Information

Sample Type		Time Postdose
Plasma	Cycle 1	Predose (within 0.5 hour before dosing) on Days 1, 8, and 15. On Day 1 of Cycle 1, samples will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, and 168 hours (predose Day 8) following the first dose.
	Cycle 2	Predose (within 0.5 hour before dosing) on Days 1, 8, and 15. Sample will be collected on Day 22 (168 hours postdose on Day 15) in Cycle 2.
	Cycle 3	Predose (within 0.5 hour before dosing) on Days 1, 8, and 15. On Day 15 of Cycle 3 following the third dose, samples will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 168 and 312 hours postdose in Cycle 3.

PK parameters of ixazomib will be derived using non-compartmental analysis methods. The PK parameters of ixazomib will be determined from the plasma concentration-time data from all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters may be determined, as permitted by the data, from concentrations of ixazomib in plasma: maximum observed plasma concentration (C_{max}), time of first occurrence of C_{max} (t_{max}), area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}) and area under the plasma concentration-time curve from time 0 to 168 hours (AUC_{168}).

Pharmacodynamics:

Changes in the levels of anti-dsDNA antibodies, complement C3/C4 levels, and UPCR.

Exploratory Assessments:

Company Confidential Information

Laboratory tests:

Clinical laboratory tests including hematology, urinalysis, and blood chemistry will be performed at Screening and during the 3-month Double-Blind Treatment Period, and the Open-Label Treatment Extension Period and follow-up periods.

Estimated total volume of blood drawn:

453.5 mL (during the Double-Blind Treatment Period and Follow-up)

493.5 mL (during the Double-Blind Treatment Period, Open-Label Treatment Extension Period, and Follow-up)

Statistical Considerations:

Safety:

Safety summaries will be performed for each dose cohort.

All AEs will be presented in listings. Treatment-emergent AEs will be summarized for each ixazomib dose level and placebo.

Baseline, postdose and change from Baseline to postdose laboratory data will be summarized for each ixazomib dose level and placebo. Individual results of laboratory tests from hematology, chemistry and urinalysis that meet

Takeda Development Center Americas, Inc. (TDC) markedly abnormal criteria to be defined in the statistical analysis plan (SAP) will be listed and summarized for each ixazomib dose level and placebo.

Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized for each ixazomib dose level and placebo. Individual results of vital signs that meet TDC's markedly abnormal criteria to be defined in the SAP will be listed and summarized by ixazomib dose level and placebo.

Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed and observed values and changes from Baseline in quantitative ECG parameters will be summarized for each ixazomib dose level and placebo. Individual results of ECG parameters that meet TDC's markedly abnormal criteria to be defined in the SAP will be listed and summarized by ixazomib dose level and placebo. Individual results of safety ECG parameters will be listed

The placebo group mentioned in the safety summaries will be the pooled placebo subjects from all cohorts. Physical examination findings will be presented in data listings.

PK Measures:

Concentrations of ixazomib in plasma will be summarized by ixazomib dose level at each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. PK parameters of ixazomib will be summarized by ixazomib dose level and subject using descriptive statistics. Dose proportionality will be assessed graphically and using the power model. Company Confidential Information

Pharmacodynamics and Exploratory Endpoints:

Pharmacodynamic and exploratory measurements will be listed and summarized as appropriate by time points for each ixazomib dose level and placebo. Additional statistical analyses will be conducted if applicable.

Sample Size Justification:

This study is not statistically powered for any hypothesis testing. The sample size of 4 active and 1 placebo in Cohorts A and B, 6 active and 2 placebo in Cohorts C and D is considered to be sufficient to fulfill the study objectives of the evaluation of safety, tolerability, and PK of each cohort.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

TDC will select a Signatory Principal Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

λz terminal elimination rate constant

AE adverse event

ACR American College of Rheumatology

ALT alanine aminotransferase ANA antinuclear antibodies

anti-dsDNA antibody to double-stranded DNA

AST aspartate aminotransferase

AUC₂₄ area under the plasma concentration-time from 0 to 24 hours

AUC₁₆₈ area under the plasma concentration-time curve from 0 to 168 hours

AZA azathioprine

BILAG British Isles Lupus Assessment Group

BMI body mass index BSA body surface area CI confidence interval

C_{max} maximum observed plasma concentration

CrCl creatinine clearance
CS clinically significant

CTCAE Common Terminology Criteria for Adverse Events

CYC cyclophosphamide
CYP cytochrome P-450
DDI drug-drug interaction
DLT dose-limiting toxicity

dsDNA double-stranded deoxyribonucleic acid

eCRF electronic case report form

eGFR estimated glomerular filtration rate

ECG electrocardiogram
ESRD end-stage renal disease
EOT End of Treatment
ET Early Termination

FACT functional assessment of cancer therapy

FDA Food and Drug Administration
FSH follicle-stimulating hormone
GCP Good Clinical Practice
GFR glomerular filtration rate

GI gastrointestinal
GN Glomerulonephritis

HBsAg hepatitis B surface antigen hCG human chorionic gonadotropin

HCV hepatitis C virus

IB Investigator's Brochure

ICH International Conference on Harmonisation

IEC independent ethics committee

IgImmunoglobulinIgAImmunoglobulin AIgGimmunoglobulin GIgMimmunoglobulin MIRBinstitutional review board

ISN International Society of Nephrology

ISV insufficient sample volume

IVRS/IWRS interactive voice response system/interactive web response system

K₂EDTA dipotassium ethylenediamine-tetraacetic acid

LLN lower limit of normal LN lupus nephritis

MedDRA Medical Dictionary for Regulatory Activities

MMF mycophenolate mofetil
MRD multiple-rising dose
MTD maximum tolerated dose
NCS not clinically significant

NOAEL no-observed-adverse-effect level
NSAID nonsteroidal anti-inflammatory drug

PGx pharmacogenomics PK pharmacokinetic(s)

PO orally

PT preferred term
PTE pretreatment event

OTcF OT interval with Fridericia correction method

RBC red blood cell
RNA ribonucleic acid

RPS Renal Pathology Society

RRAL relapsed or refractory AL amyloidosis
RRMM relapsed and refractory multiple myeloma

SAE serious adverse event
SAP statistical analysis plan
SCr serum creatinine

SLE systemic lupus erythematosus SNP single nucleotide polymorphism

SOC system organ class

SRC Safety Review Committee $t_{1/2}$ terminal elimination half-life

TB tuberculosis

 $TEAE & treatment-emergent adverse event \\ t_{max} & time of first occurrence of C_{max} \\$

ULN upper limit of normal

UPCR urine protein to creatinine ratio

WBC white blood cell

WHO World Health Organization

3.4 Corporate Identification

TDC Asia Takeda Development Center Asia, Pte. Ltd.
TDC Europe Takeda Development Centre Europe Ltd.
TDC Americas Takeda Development Center Americas, Inc.

TDC Asia, TDC Europe and/or TDC Americas, as applicable

TPC Takeda Pharmaceutical Company Limited

Takeda TDC Asia, TDC Americas, TDC Europe, and/or TPC, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a heterogenous autoimmune disease characterized by dysregulation of T and B lineage cells, as well as other components of the innate immune system and production of autoantibodies. A hallmark of the disease is the production of pathogenic autoantibodies to double-stranded deoxyribonucleic acid (dsDNA), phospholipids, blood cells and other targets. Tissue damage in SLE is caused primarily by these pathogenic autoantibodies through immune complex deposition with Fc- and complement mediated inflammation, as well as through direct antibody-target interactions [1]. Virtually any organ or system in the body can be affected by SLE [2,3]. The estimated prevalence of SLE ranges from 40 cases per 100,000 among Northern Europeans to 200 cases per 100,000 among blacks [1]. SLE affects approximately 280,000 adults in the United States, with an estimated prevalence rate of 129 per 100,000 in adults aged 18 years and over [4]. The incidence rates of SLE range from approximately 1 to 10 per 100,000 person-years around the world [5]. Disease onset is more common between the third and fourth decade of life and 90% of patients with SLE are females.

4.1.2 Lupus Nephritis

Lupus nephritis (LN), an inflammatory autoimmune disease of the kidney caused by SLE, is the most common life-threatening manifestation of systemic lupus. Approximately 60% of the SLE patients will develop renal involvement during the course of disease, with substantial morbidity or mortality either secondary to kidney disease or toxicities related to intensive immunosuppressive drug regimens [6,7]. The prevalence of LN is significantly higher in African Americans and Hispanics than in whites, and is higher in women than in men [8].

A diagnosis of LN can be made in subjects with SLE if clinical and laboratory manifestations meet any of the American College of Rheumatology (ACR) criteria. LN can be divided in 6 classes and several subclasses (Appendix I), according to the World Health Organization (WHO) and the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classifications [6]. Glomerulonephritis (GN) is the most common form of renal disease in SLE, but is frequently accompanied by tubulointerstitial and vascular lesions. Proliferative GN classes III and IV are the most severe manifestations of renal pathology and the ones requiring aggressive immunosuppressive treatment to prevent progression to end-stage renal disease (ESRD) and minimize associated morbidity and mortality. LN Class III by glomerular pathology is defined as focal LN involving less than 50% of all glomeruli and Class IV is defined as diffuse LN involving 50% or more of glomeruli in the biopsy [6,7]. Standard of care in subjects with ISN/RPS class III/IV LN is not universal, but generally consists of an induction period of more intensive therapy to achieve meaningful and sustained responses, followed by a less intensive maintenance therapy in responders. The ACR Task Force Panel recommend mycophenolate mofetil ([MMF], 2 to 3 g total daily orally) or intravenous cyclophosphamide (CYC) along with glucocorticoids for induction therapy for a period of 6 months. Subjects who achieve partial or

complete response to induction therapy are then placed on maintenance regimens with either azathioprine or MMF. In subjects who fail to respond after 6 months to treatment with glucocorticoids plus CYC or MMF, the Task Force Panel recommends a switch to an alternative immunosuppressive agent, with these changes accompanied by intravenous pulses of glucocorticoids for 3 days [8]. Alternative agents include rituximab, a chimeric monoclonal antibody against the protein monoclonal antibody CD20, calcineurin inhibitors, cyclosporine, and recently tacrolimus [8].

In addition, a recent study retrospectively analyzing a trial showed that after 8 weeks of induction treatment with either CYC or MMF, subjects with LN who showed a 25% reduction in proteinuria and/or normalization of C3 and/or C4 were likely to show good clinical renal response [9]. Similarly, after 6 months of treatment, a decrease in serum creatinine and in proteinuria to 1 gram/24 hours predicts good long-term outcomes. Therefore, if a patient is not meeting these targets at 3 or 6 months it may be appropriate to modify treatment [10].

Despite improvements in standard of care therapy only 25% to 50% of patients achieve full remission by 2 years and the majority experiences a relapse within 5 years, with 10% to 20% progressing to end-stage renal disease requiring dialysis and / or kidney transplantation [11]. Moreover, existing therapies cause significant drug-related morbidity and use of glucocorticoids is one of the major causes of organ damage in patients with SLE [12].

Class V GN is also associated with chronic kidney disease and ESRD. Decreased glomerular filtration rate (GFR) occurs in about 20% of cases and ESRD in about 8-12% after 7-12 years. In one small RCT trial examining the treatment of class V LN patients responded to immunosuppression but failure to achieve sustained remission was a risk factor for decline in renal function. The Kidney Disease Improving Global Outcomes recommends that patients with class V and persistent nephrotic proteinuria be treated with corticosteroids plus an additional immunosuppressive agent CYC, CNI, MMF or azathioprine [13].

Pathogenic autoantibodies produced by B cells, plasmablasts and plasma cells are critically involved in SLE pathogenesis, particularly LN, where renal deposition of immune complexes is a hallmark of the disease. Current available treatments can at different levels target B cells, plasmablasts and short-lived plasma cells, although long-lived plasma cells remain resistant to these treatments, and even to autologous and allogeneic stem cell transplantations [14,15].

4.1.3 Proteasome Inhibition in SLE and LN

Proteasomes are intracellular enzyme complexes which play a key role in degradation of a variety of proteins, including many that regulate cell cycle, adhesion, angiogenesis, cytokine production, and apoptosis. Proteasome inhibitors have antiproliferative effects on activated immune cells by inhibiting the proteasomal degradation of numerous regulatory ubiquitinated proteins. Proteasome inhibition also results in the accumulation of poly-ubiquitinated substrates within the cell leading to cell cycle disruption, with concomitant activation of apoptotic pathways, cell death, and the UPR [16]. Cells with high protein synthesis such as plasmablasts and plasma cells are particularly sensitive to proteasome inhibition [17]. Additionally, proteasome inhibitors also suppress survival and immunostimulatory functions of human

plasmacytoid dendritic cells, which play a central role in SLE, by producing high levels of IFN- α , interfering with Toll-like receptor intracellular trafficking and endoplasmic reticulum homeostasis [18].

Nonmalignant plasma cells, which are key contributors to autoantibody production, are known to be depleted by bortezomib (VELCADE), a 20S proteasome inhibitor currently approved for the treatment of multiple myeloma and which is administered intravenously or subcutaneously. Nonclinical evidence of efficacy of proteasome inhibition in SLE and LN was demonstrated in the NZB/W F1 and MRL/lpr mouse models of SLE. Treatment with bortezomib reduced antibody to double-stranded DNA (anti-dsDNA) antibodies, reduced proteinuria and kidney damage, and prolonged survival [19,20].

Importantly, reduction or even normalization of proteinuria was observed in the subjects with LN. Proteasome inhibition may therefore be a useful approach to removing the

plasma cells that produce pathogenic autoantibodies involved in LN.

4.1.4 Proteasome Inhibitor Ixazomib

Ixazomib citrate is an orally active, small molecule proteasome inhibitor. Ixazomib citrate refers to the citrate ester of ixazomib. In water or aqueous systems, the equilibrium shifts from ixazomib citrate to the biologically active boronic acid form, ixazomib. Ixazomib is a potent reversible inhibitor of the 20S proteasome in mammalian cells, inhibiting β5 site 20S proteasome activity in vitro with a 50% inhibitory concentration of 3.4 nM (1.2 ng/mL). In both animals and in humans, extensive red blood cell (RBC) partitioning was noted. In Study C16007, plasma and whole blood pharmacokinetic (PK) profiles of ixazomib were compared and concentrations were higher in blood than plasma throughout the dosing interval.

Ixazomib demonstrates strong antitumor activity in xenograft models derived from human cancer cell lines or primary human tumors. It also reduces anti-keyhole limpet hemocyanin and anti-dsDNA antibodies, plasma cell, and plasmacytoid dendritic cell populations in animal models comparable to that for bortezomib, supporting efficacy in LN.

Ixazomib has potential advantages over bortezomib, including oral administration, dosing independent of body size, and, as observed in the current oncology program, a reduced propensity for the neuropathy. Ixazomib is currently under investigation in 3 phase 3 registration studies including relapsed and refractory multiple myeloma (RRMM), newly diagnosed multiple myeloma, and relapsed amyloid light-chain (AL) amyloidosis.

4.1.4.1 Nonclinical Toxicology

A total of 10 repeat-dose toxicity studies have been completed with ixazomib with intravenous (IV) or oral (PO) administration to Sprague-Dawley rats and beagle dogs. For the repeat-dose toxicity studies of up to 10 cycles of twice a week dosing (20 doses over 95 days), one 21-day cycle consisted of twice a week dosing for 2 weeks; multiple cycles were separated by a 10-day

nondosing period. The doses used in the rat studies were 0.2, 0.4, and 0.8 mg/kg (reduced to 0.6 mg/kg after the first 2 cycles). In the dog studies, doses were 0.05, 0.10, and 0.20 mg/kg.

The toxicity of ixazomib was evaluated in Sprague-Dawley rats administered ixazomib via PO gavage (0, 0.2, 0.4, 0.8/0.6 mg/kg/dose) for 6 months (7 dosing cycles, with each 28-day cycle consisting of once weekly doses for 3 consecutive weeks separated by a 13 day non-dosing period). Cycle 7 was followed by a 2-week recovery period (WIL-416165). The target organs identified were the gastrointestinal (GI) tract and lymphoid organs, with findings either fully or nearly reversible.

Five females in the 0.8/0.6 mg/kg/dose group died between Days 9 to 170 and the cause of death was determined to be likely due to the young age of the animals (7 weeks of age), higher exposures compared to male rats, and test article-related findings in the intestine, liver, and lymphoid organs. At all doses, there were minimal-to-moderate, dose-dependent effects in the GI tract, which included epithelial hyperplasia, neutrophilic infiltrates, and single cell necrosis in the lamina propria in the small and large intestines. The changes observed at 0.2 mg/kg/dose were minimal and fully reversible. At ≥ 0.4 mg/kg/dose, minimal-to-moderate changes included increases in mandibular salivary gland mucin and inflammation of the glandular/nonglandular stomach and, at the highest dose, erosion and ulceration of the glandular and nonglandular stomach, respectively. At ≥ 0.4 mg/kg/dose, hematological changes (increased white blood cells, neutrophils, lymphocytes, monocytes, and basophils), reduced body weight gains, and clinical signs (diarrhea, small/soft/decreased feces, hypoactivity, thin appearance, and yellow material around the urogenital/anogenital areas and forelimbs) correlated with GI changes.

Dose-dependent, minimal-to-mild changes in lymphoid organs were reported at \geq 0.2 mg/kg/dose and included mesenteric lymphoid necrosis, neutrophilic infiltrates in the spleen (red pulp), and bone marrow hypocellularity. Minimal-to-mild microscopic effects were reported in the endocrine system (decreased vacuolation of the zona fasciculata of the adrenal cortex), reproductive tissues (increased lobulo-alveolar hyperplasia and increased secretion of the mammary gland, spermatid retention in the testes), and blood vessels (mononuclear perivasculitis of the meninges of the brain and spinal cord and the submucosa of the intestine). Although it is uncertain if these microscopic findings were treatment-related, they were fully reversible after the 2-week recovery period. Based on the results of this study, the no-observed-adverse-effect-level (NOAEL) was determined to be 0.2 mg/kg/dose in males and females. At this dose, the mean maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 168 hours (AUC₁₆₈) values (Day 168) for males:females (M:F) were 5.42:6.55 ng/mL and 489:476 ng·hr/mL, respectively.

The toxicity profile of ixazomib was evaluated in beagle dogs via PO gavage (0, 0.05, 0.10, and 0.20 mg/kg/dose) for 9 months (10 dosing cycles, with each 28-day cycle consisting of 3 once weekly doses separated by a 13 day nondosing period). Cycle 10 was followed by a 2-week recovery period (WIL-416164). Test article-related organ toxicity was reported in the GI tract, lymphoid tissues, and peripheral nervous system (PNS).

There were no deaths in this study. At \geq 0.10 mg/kg/dose, minimal test article-related effects were reported in the GI tract and lymphoid tissue and included neutrophilic infiltration in the

stomach, intestines, mesenteric lymph node and/or Peyer's patches, and stomach erosions. The neutrophilic infiltrates correlated with increased white blood cells, neutrophils, and monocytes. The erosion in the stomach and the neutrophilic infiltration were fully or nearly reversible at the end of the 2-week recovery period. In the PNS at 0.20 mg/kg/dose, test article-related findings included neuronal degeneration of the sympathetic, dorsal root, and end organ ganglia, secondary axonal/nerve fiber degeneration of the peripheral nerves (vagus and sciatic nerves, dorsal roots and mixed spinal nerves), ascending tracts in the dorsal column of the spinal cord and white matter tracts in the medulla oblongata, gliosis of the dorsal column of the spinal cord and white matter tracts in the brain, with the latter two secondary to axonal degeneration of the ascending tracts. At the end of the 2-week recovery period, the only neuronal findings were nerve fiber degeneration of the dorsal root ganglion and an increase in axonal degeneration in the dorsal columns of the spinal cord. The lack of ongoing neuronal degeneration and no changes in the functional observational battery are indicative of no persistent neuronal toxicity and no functional impact on the nervous system. In addition to these findings, decreased lymphocyte counts, increased aspartate aminotransferase, and decreased serum phosphorus were reported at 0.20 mg/kg/dose. Based on these findings, the NOAEL was determined to be 0.10 mg/kg/dose in males and females. At this dose, the mean C_{max} and AUC₁₆₈ values (Day 252) were 136 ng/mL and 1940 ng·hr/mL, respectively.

In summary, the target tissues for rats and dogs were similar and consisted of the bone marrow, peripheral ganglia, GI tract, and lymphoid tissues. In the longer cycle, repeat-dose toxicity studies, the kidney, adrenal, lacrimal, and perianal glands were identified as target organs in either the rat or dog. The most sensitive hematology indicator of a test article-related effect in rats was thrombocytopenia and, in dogs, decreased reticulocyte counts. Peripheral ganglia effects, although qualitatively similar in rats, were more severe in dogs. All of the effects seen in both rats and dogs were fully or nearly reversible.

4.1.4.2 Drug Metabolism and PK

Ixazomib citrate is hydrolyzed to the boronic acid form ixazomib which is mainly cleared via metabolism; clinical PK data indicate that renal clearance contributes little to the total elimination of ixazomib (≤10% is renally cleared following intravenous administration). Consistently, no relationship between creatinine clearance (CrCl) and systemic clearance has been observed in the preliminary population PK analysis (N=137) over a wide range of renal function categories (CrCl range: 22-236 mL/min). Therefore, it is expected that there will be no increases in ixazomib exposures when administered to subjects with mild to moderate renal impairment [21,22].

In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P-450 (CYPs) and non-CYP enzymes/proteins. At clinically relevant concentrations of ixazomib, in vitro studies using human complementary DNA-expressed CYP isozymes showed that no specific CYP isozyme predominantly contributes to ixazomib clearance. At concentrations exceeding those observed clinically (10 μ M), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%) and 2C9 (<1%). In contrast, at 0.1 μ M and 0.5 μ M substrate concentrations,

which are closer to clinical concentrations of ixazomib, non-CYP-mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, minimal CYP-mediated drug-drug interactions (DDIs) with a selective CYP inhibitor would be expected. In addition, ixazomib is neither a reversible nor a time-dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Prednisone and MMF treatment is allowed in this study. Prednisone is metabolized via CYP3A4 and is a known inducer of CYP2C19, MMFs major metabolic pathway is mediated via glucuronosyltransferases; therefore, the likelihood of a drug interaction with ixazomib in both cases is considered to be low. Overall, the potential for ixazomib treatment to produce DDIs via CYP inhibition is inferred to be low.

In a phase 1 DDI study, the PK of ixazomib was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor (Study C16009, Arm 5); hence, no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors [21]. These findings are explained by the in vitro metabolism data indicating the lack of a discernible contribution of CYP-mediated metabolism at clinically relevant ixazomib concentrations. As discussed earlier, no CYP isoforms have been identified to contribute meaningfully to ixazomib metabolism at clinically relevant concentrations and CYP3A contribution to total metabolism was highest across all CYP isoforms when characterized at a supratherapeutic concentration of 10 µM. Therefore, based on the totality of information from the clinical clarithromycin DDI study and the in vitro CYP phenotyping data, it can be concluded that ixazomib PK is not likely to be altered upon co-administration with any CYP isoform-selective inhibitor, including strong CYP1A2 inhibitors. Consistently in the population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance [22]. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2.

In a phase 1 DDI study, coadministration of ixazomib with rifampin decreased ixazomib C_{max} by 54% and area under the plasma concentration-time curve by 74% (Study C16009, Arm 4) [21]. Accordingly, concomitant administration of ixazomib with strong CYP3A inducers should be avoided (see Section 7.3). Please refer to the prescribing information for ixazomib for further details [23].

4.1.4.3 Clinical Experience

Ixazomib is currently in phase 3 development for oncology indications. As of the 27 March 2013 data cut, 637 oncology subjects have received at least 1 dose of ixazomib either as a single agent or in combination with regimens commonly used in clinical practice for the particular malignancy (safety population). A total of 146 subjects were enrolled in IV studies and 491 in uncontrolled studies with oral ixazomib. Additionally, 817 subjects have been treated with oral ixazomib or placebo in blinded phase 3 trials. For initial studies with ixazomib the IV doses ranged from 0.125 to 3.11 mg/m² and PO doses ranged from 0.24 to 3.95 mg/m² with once or twice weekly dose schedules. For the ongoing and planned studies, a weekly administration schedule is used that consists of dosing on Days 1, 8, and 15 followed by a 13-day drug holiday, which allows for adverse event (AE) recovery before starting the next planned cycle.

Ixazomib has been evaluated as a single agent in phase 1 studies that have included subjects with advanced solid tumors (C16001, IV, and C16009, PO), lymphoma (C16002, IV), RRMM (C16003 and C16004, PO) and relapsed or refractory AL amyloidosis (RRAL) (C16007, PO). The actual initial doses of oral ixazomib used in the oncology program ranged from 0.2 to 10.6 mg (as a single-agent from 0.2 to 8.9 mg; in combination studies from 2.9 to 10.6 mg) and fixed doses of 3.0 to 5.5 mg. The initial doses of IV ixazomib used in the single-agent oncology studies (both twice weekly and weekly) ranged from 0.2 to 6.8 mg (weekly only from 0.23 to 6.8 mg). Maximum tolerated doses (MTDs) determined in the oncology studies ranged between 4.0 and 5.5 mg. Pooled mean (SD) number of cycles in 9 PO and 2 IV dosing studies combined for oncology is 5.4 (5.85) cycles, [median 3.0, range 1-46]. In the 9 PO studies, the mean (SD) number of cycles is 6.4 (6.16) [range 1-46] and in the 2 completed IV studies the mean (SD) was 3.0 (4.05) [range 1-34] treatment cycles.

The emerging safety profile indicates that ixazomib is generally well tolerated with manageable and reversible AEs with both the IV and PO formulations. The types of AEs reported are similar for the 2 formulations, yet the frequency and severity differ. Refer to the ixazomib Investigator's Brochure (IB) for details on ixazomib safety experience and doses ranges used. The adverse drug reactions that occurred at ≥10% in the single-agent oral administration studies include thrombocytopenia, diarrhea, nausea, vomiting, fatigue, pyrexia, and skin rash. Additional adverse drug reactions that occurred at ≥10% in the oral combination therapy studies include anemia, neutropenia, constipation, dysgeusia, neuropathy peripheral, and insomnia. Adverse effects reported in the clinical studies with ixazomib to date may have been due to the subject's underlying disease, treatment with ixazomib, other medications, or some combination of these. The observed AEs are generally consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with bortezomib. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention.

Table 4.a outlines the most common AEs regardless of grade or causality reported across dose levels which are approximately equivalent to those proposed for this study. Fatigue, thrombocytopenia, diarrhea, nausea, and vomiting were reported. At doses higher than proposed in this study all of these common AEs were reported in at least 45% of the subjects. Looking at pooled data across the lower doses, only fatigue, which may have been due to either disease, study drug, or both, was reported at this rate. Additionally, no subject treated at the lower doses experienced an AE which required a dose reduction; whereas 45% of those treated at the MTD (2.97 mg/m² [~ equivalent to 5.5 mg fixed]) did experience an AE requiring a dose reduction.

Table 4.a Study C16004 Most Common (>30% of Subjects in MTD Cohort) AEs Regardless of Causality by Dose Cohort

Number of Subjects/AE Number of Subjects/CTCAE Grade

	Ixazomib Dose				
MedDRA Preferred Term	0.48 mg/m ² (~ equivalent to mg fixed) N=3	1.2 mg/m ² 1 (~ equivalent to mg fixed) N=3	1.68 mg/m ² 2 (~ equivalent to mg fixed) N=4	2.23 mg/m ² 3 (~ equivalent to 4 mg fixed) N=3	2.97 mg/m ² (~ equivalent to 5.5 mg fixed) N=31
Fatigue	2 2/Grade 2	2 1/Grade 1 1/Grade 2	2 2/Grade 1	0	17 2/Grade 1 10/Grade 2 5/Grade 3
Thrombocytopenia	1 1/Grade 2	2 1/Grade 1 1/Grade 3	1 1/Grade 3	1 1/Grade 3	17 1/Grade 1 1/Grade 2 5/Grade 3 10/Grade 4
Diarrhea	0	0	0	2 2/Grade 1	17 4/Grade 1 6/Grade 2 7/Grade 3
Nausea	1 1/Grade 1	1 1/Grade 1	1 1/Grade 2	1 1/Grade 1	15 9/Grade 1 5/Grade 2 1/Grade 3
Vomiting	1 1/Grade 1	0	0	2 2/Grade 1	14 10/Grade 1 3/Grade 2 1/Grade 3
Decreased appetite	0	0	0	0	14 6/Grade 1 4/Grade 2 4/Grade 3
Neutropenia	0	0	0	0	11 3/Grade 2 8/Grade 3

Source: Ixazomib IB version 8; C16004 CSR Table 14.4.1.4.

CTCAE=Common Terminology Criteria for Adverse Events v. 4.0, MedDRA=Medical Dictionary for Regulatory Activities.

In study 16005, where weekly ixazomib was given in combination with a standard dose of lenalidomide and dexamethasone in a 28-day cycle, the MTD was defined as 2.97 mg/m². The dose-limiting toxicities (DLTs) at the dose level above MTD (3.95 mg/m²) were dizziness, orthostatic hypotension, nausea, vomiting, syncope in 3/3 subjects and Grade 2 peripheral neuropathy in 1 subject. At this dose, the actual initial doses of ixazomib administered were 8.2 to 10.6 mg. The DLT at the 2.97 mg/m² dose level was rash in 1/6 subjects, where the initial

doses of ixazomib administered were 4.6 to 6.2 mg. The recommended phase 2 dose estimation was established following evaluation of the available data from the phase 1 portion of this study, which included, but was not limited to, analyses of efficacy results and safety (Grade 3/4 AEs, serious adverse events [SAEs], all grades of peripheral neuropathy, and treatment discontinuation). Given that the dose of 2.97 mg/m² ixazomib compromised the maximal dosing of lenalidomide and that the dose of 2.23 mg/m² (approximately equivalent to a 4 mg fixed dose) was well tolerated and clinically active, the 2.23 mg/m² dose was designated as the recommended phase 2 and 3 dose. The actual initial doses of ixazomib administered to the subjects in the 2.23 mg/m² Cohort were 3.4 to 4 mg.

As can be noted in Table 4.b, in most of the phase 1 PO studies, this dose was determined as the MTD for ixazomib, either as a single agent or in combination with standard oncology treatments, when given once weekly 3 out of 4 weeks in a 28-day cycle. DLTs across these studies were also similar and primarily included thrombocytopenia and GI symptoms (nausea, vomiting, and diarrhea).

The relevant clinical studies following oral weekly administration of ixazomib citrate are illustrated in Table 4.b.

Table 4.b Summary of MLN9708 (ixazomib) Clinical Oncology Studies With Once Weekly Oral Dosing

Trial/ Population	Description	Doses Investigated
C16004 Phase 1 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m ² MTD: 2.97 mg/m ² (4.4 to 7.2 mg) DLT: rash, nausea, vomiting, diarrhea Closed to enrollment Median # cycles: 2.0 (range 1,12)
C16005 Phase 1/2 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m ² MTD: 2.97 mg/m ² (4.6 – 6.2 mg) DLT: nausea, vomiting, diarrhea, syncope, rash, dizziness, orthostatic hypotension, and 1 patient with Grade 2 peripheral neuropathy RP2D (a): 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23 mg/m ²) Closed to enrollment Median # cycles: 7.0 (range 1,27)
C16006 Phase 1/2 NDMM N = 25	PO, TW, Arm A-42-day cycle and W, Arm B- 28-day cycle combination with melphalan and prednisone 28-day cycle	Arm A: 3.0-3.7 mg fixed dose TW DLT: rash, thrombocytopenia, subileus MTD: 3.0 mg Arm B: 3-5.5 mg fixed dose W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 4.0 mg Median # cycles: 7.5 (range 1,19)

Footnotes are on last table page.

Table 4.b Summary of MLN9708 (ixazomib) Clinical Oncology Studies With Once Weekly Oral Dosing (continued)

Trial/ Population	Description	Doses Investigated
C16007 Phase 1 RRAL N = 27	PO, W, single agent	4-5.5 mg fixed dose (a) DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, non-fatal cardiac arrest Closed to enrollment MTD: 4.0 mg Median # cycles: 4.0 (range 1,12)
C16009 Phase 1 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5 mg fixed dose (a) Study amended to a 4.0 mg fixed dose (a) with allowance for increase to 5.5-mg if tolerated after Cycle 4 Median # cycles: 2.0 (range 1,9)
C16010 Phase 3 RRMM N=54	PO, W, with LenDex versus placebo LenDex	+ 4.0 mg fixed dose Dex 40 mg PO days 1, 8, 15, and 22 Len 25 mg days 1-21 of a 28-day cycle Ongoing
C16011 Phase 3 RRAL N=4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg fixed dose
C16013 Phase 1 RRMM N=10	PO, W, combination with LenDex 28 day cycle.	- 4.0 mg, 5.5 mg fixed doses (a) DLT: diarrhea, hypertension, hypokalemia, hyponatremia, nausea, thrombocytopenia Single agent MTD 4.0 mg MTD in combination with LenDex 28-day cycle-TBD Median # cycles: 2.0 (range 1,3)

Source: Ixazomib IB version 8.

Dex=dexamethasone, LenDex = lenalidomide plus dexamethasone, NDMM = newly diagnosed multiple myeloma, TBD=to be determine, TW= twice weekly, W=weekly.

(a) Approximate body surface area (BSA) and fixed dosing equivalence: $3 \text{ mg} \sim \text{equivalent to } 1.68 \text{ mg/m}^2 \text{ BSA dosing}$; $4.0 \text{ mg} \sim \text{equivalent to } 2.23 \text{ mg/m}^2 \text{ BSA dosing}$; and $5.5 \text{ mg} \sim \text{equivalent to } 2.97 \text{ mg/m}^2 \text{ BSA dosing}$.

As of 27 March 2014, out of the safety population in studies with oral ixazomib, 50 patients reported 68 AEs at least possibly related to study treatment that resulted in study drug discontinuation. The most common of these events were rash (7 patients), peripheral neuropathy or peripheral sensory neuropathy (6 patients), renal impairment/failure (6 patients), fatigue/asthenia (6 patients), and thrombocytopenia (5 patients). Furthermore, at least 1 SAE has been reported for 474 subjects (36%) across all Takeda-sponsored clinical studies in oncology (including ongoing Phase 3 trials) using oral or placebo/control in combination with standard therapies. The reported SAEs include effects attributable to disease progression and those related to study treatment. Regardless of causality, the most common SAEs included pneumonia (62 subjects) and pyrexia (30 subjects). As of 27 March 2014, a total of 42 patients died on study (ie, within 30 days after last dose) across all clinical studies in oncology with the oral formulation of ixazomib. The most common cause of death in the studies was disease

progression. Six deaths were considered at least possibly related to study treatment: 2 occurred in open label trials (1 each respiratory syncytial viral pneumonia and cardiopulmonary arrest, both of which occurred in clinical trials combining oral ixazomib plus LenDex), and 4 occurred in ongoing blinded trials of oral ixazomib or placebo plus LenDex.

4.2 Rationale for the Proposed Study

Proteasome inhibition using ixazomib is a novel mechanism of action for the treatment of LN as compared to the drugs currently used [24]. Proteasome inhibitors have been approved for use in plasma cell malignancies such as multiple myeloma. Non-malignant plasma cells are also sensitive to proteasome inhibition, and these cells play a key role in several autoimmune diseases, including SLE and LN. Both nonclinical and clinical data support further investigation of proteasome inhibitors such as ixazomib in LN.

This study is a phase 1b, randomized, double-blind, placebo-controlled, safety, tolerability, and PK study of multiple-rising doses (MRD) of ixazomib for the treatment of subjects with ISN/RPS Class III, IV or V changes [excluding Class III (C), IV-S (C) and IV-G (C)] or WHO 1982 classification of Class III, IV or V (excluding Class IIIc and IVd). It is anticipated that 4 ixazomib dose levels will be examined. At least 5 subjects (4:1) will be recruited into the 0.5 mg dose group (Cohort A), at least 5 subjects (4:1) in the 2.0 mg dose group (Cohort B), 8 subjects (6:2) in the 3.0 mg dose group (Cohort C), and 8 subjects (6:2) in the 4.0 mg dose group (Cohort D). Subjects will be considered eligible on the basis of study inclusion and exclusion criteria, verified by an independent adjudication committee, and randomized. Following each of the 0.5, 2.0, and 3.0 mg dose cohorts, available PK and safety data will be evaluated before escalation. For each dose level cohort, the Safety Review Committee (SRC) will carefully review the available safety, tolerability, and PK data to determine if dosing should be escalated in the next cohort, lowered or expanded within the same dose cohort to obtain additional information before a dose-escalation decision, or stopped. After 5 subjects are recruited in the 4.0 mg dose group (Cohort D) and complete at least 1 cycle of ixazomib or placebo, an analysis may be conducted on available PK data and blinded safety data from all cohorts. Subject numbers may be increased as appropriate per cohort for a total number not exceeding 40 subjects in all cohorts combined. Two subjects with Class V or Class V with Class II nephritis are permitted per cohort. Subjects will be treated with three 28-day cycles of ixazomib or placebo during the Double-Blinded Treatment Period.

This study will provide initial information on the safety and tolerability of ixazomib over 3 double-blind dosing cycles in subjects who have inadequately responded to at least 3 months of an immunosuppressive regimen including single or sequential use of CYC, MMF, mycophenolic acid (MA) or azathioprine (AZA). In addition, this phase 1b study will provide data to guide dose-range selection for further studies, along with exploratory biomarker and pharmacogenomic analyses which may aid subject stratification for future studies.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

To characterize the safety and tolerability of ixazomib when administered as multiple oral doses at escalating dose levels in subjects with LN.

5.1.2 Secondary Objectives

- To assess changes from Baseline in urine protein to creatinine ratio (UPCR) in LN subjects following multiple administrations of ixazomib.
- To evaluate the effect of ixazomib on kidney function, as assessed by changes from Baseline in serum creatinine (SCr) and estimated glomerular filtration rate (eGFR).
- To evaluate the effect of ixazomib on anti-dsDNA antibody titers and complement C3/C4 levels.
- To characterize the plasma PK of ixazomib in LN subjects when ixazomib is administered over 3 cycles consisting of 3 doses per cycle.

5.2 Endpoints

5.2.1 Primary Endpoints

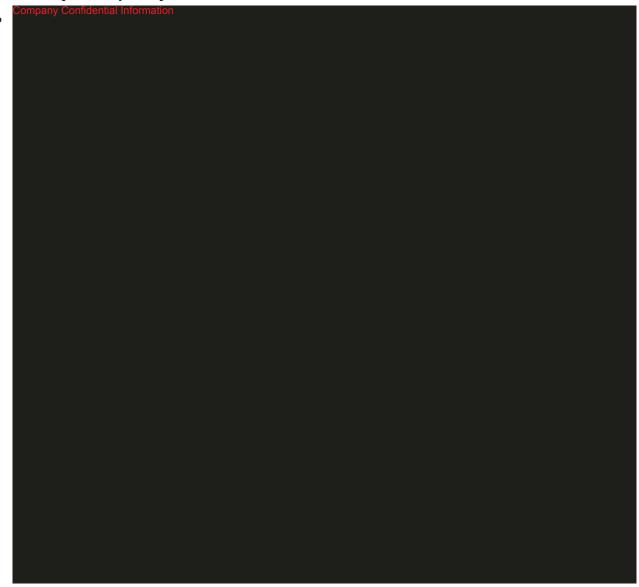
- Percentage of study subjects with at least 1 Grade ≥2 treatment emergent adverse event (TEAE) according to CTCAE.
- Percentage of study subjects with at least 1 SAE.
- Percentage of study subjects with at least 1 AE leading to discontinuation of investigational study medication.
- Percentage of subjects with at least 1 markedly abnormal laboratory criteria for hematologic parameters.

5.2.2 Secondary Endpoints

- Change from Baseline to Final Visit of Double-Blind Treatment Period in UPCR.
- Change from Baseline to Final Visit of Double-Blind Treatment Period in SCr level.
- Change from Baseline to Final Visit of Double-Blind Treatment Period in eGFR measurement
- Change from Baseline to Final Visit of Double-Blind Treatment Period in levels of autoantibodies (anti-dsDNA) and complement (C3 and C4).

- Plasma PK of ixazomib in subjects with LN following administration of ixazomib in the Double-Blind Treatment Period.
 - Plasma PK endpoints will be the following PK parameters of ixazomib in all cohorts:
 - Maximum plasma concentration (C_{max}).
 - time of first occurrence of $C_{max}(t_{max})$.
 - Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration (AUC_(0-tlqc)); or AUC₁₆₈, if measurable.

5.2.3 Exploratory Endpoints



Company Confidential Information

5.2.4 Additional Safety Endpoints

Safety assessments will be based on AE reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, and clinical laboratory tests.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This study is a phase 1b, randomized, double-blind, placebo-controlled, safety, tolerability, and PK MRD of ixazomib for the treatment of subjects with ISN/RPS Class III, IV or V changes [excluding Class III (C), IV-S (C), and IV-G (C)] or WHO 1982 classification of Class III, IV, or V (excluding Class IIIc and IVd) LN. It is anticipated that 4 ixazomib dose levels will be examined. At least 5 subjects (4:1) will be recruited into the 0.5 mg dose group (Cohort A), at least 5 subjects (4:1) in the 2.0 mg dose group (Cohort B), 8 subjects (6:2) in the 3.0 mg dose group (Cohort C), and 8 subjects (6:2) in the 4.0 mg dose group (Cohort D). Subjects will be considered eligible on the basis of study inclusion and exclusion criteria, verified by an adjudication committee, and randomized. Following each of the 0.5, 2.0, and 3.0 mg dose cohorts, available PK and safety data will be evaluated before escalation. For each dose level cohort, the SRC will carefully review the available safety, tolerability, and PK data to determine if dosing should be escalated in the next cohort, lowered, or expanded within the same dose cohort to obtain additional information before a dose-escalation decision, or stopped. After 5 subjects are recruited in the 4.0 mg dose group (Cohort D) and complete at least 1 cycle of ixazomib or placebo, an analysis may be conducted on available PK data and safety/tolerability data from all cohorts. Subject numbers may be increased as appropriate per cohort to a total number not to exceed 40 subjects in all cohorts combined. Two subjects with Class V or Class V with Class II nephritis are permitted per cohort. Subjects will be treated with three 28-day cycles of ixazomib or placebo. Subjects who successfully completed 12 weeks of double-blind treatment without any AE resulting in dose modification or discontinuation of the study drug (defined in Section 7.4.3) will be eligible to receive up to 3 additional cycles of open-label ixazomib at the discretion of the investigator and confirmed by the sponsor/designee following the end of the Double-Blind Treatment Period. The subjects need to begin the Open-Label Treatment Extension Period within 4 weeks of completing Cycle 3 of double-blind treatment.

Each 28-day cycle will consist of 3 once-weekly oral doses of 0.5, 2.0, 3.0, or 4.0 mg of ixazomib (dosage strength is stated as the active boronic acid ixazomib) or placebo, depending on the cohort. Subjects who received a dose ≤2.0 mg and completed all cycles including the Follow-up Period, will be permitted to re-enroll into the 2.0 and 3.0 mg dose groups, provided they have no drug-related AEs >Grade 1 that required the study drug dose modification, no AEs >Grade 2, continue to meet all inclusion and exclusion criteria, and the SRC (consisting of sponsor personnel and the coordinating investigator) have reviewed and approved enrollment. Subjects must be receiving standard of care treatment for LN and remain on their current stable and allowed therapies during the Screening Period and throughout the duration of the study (Section 8.1.1.2).

The study consists of the following Periods: a Screening Period (up to 35 days), a Double-Blind Treatment Period (Day 1 to Day 84) and either a Follow-up Period or an Open-Label Treatment Extension Period (Day 85 to Day 168). For those subjects who enter the Open-Label Treatment Extension Period, visits will be monthly (either for dosing or follow-up) until Day 168, with the last study visit being 30 days after the last open-label dosing or Day 168 whichever is longer.

Subjects can be randomized 24 (+11) days after Screening (between Days -24 and -35) and once safety laboratory tests and inclusion/exclusion criteria have been reviewed and confirmed by the investigator. Diagnostic criteria, disease activity measures, and treatment history will be documented, and required laboratory investigations initiated. Subject eligibility will be reviewed by an adjudication committee. The responsibilities and criteria of this committee will be defined in an adjudication charter.

Following verification of eligibility, subjects will return to the clinic on Day 1, undergo baseline assessments, laboratory testing, and will be randomized to either ixazomib or placebo within each cohort/dose level. The Double-Blind Treatment Period will consist of three 28-day treatment cycles (Cycles 1, 2, and 3) without intra-subject dose escalation. Subjects will receive ixazomib treatment on Days 1, 8, and 15 of each 28-day cycle. The second and third cycles will commence on the first day following Day 28 of the preceding cycle (ie, with a period of 13 days between the third drug administration of a cycle and the first drug administration of the following cycle). The Double-Blind Treatment Period will be limited to 3 complete cycles with ixazomib or placebo, over an expected duration of 12 weeks. However, the total treatment period may be longer than the standard 12 weeks if delays between cycles are necessary due to AEs. After completion of Cycle 3 of the Double-Blind Treatment Period, the subject will either enter the Follow-up Period or enter an optional Open-Label Treatment Extension Period at the investigator's discretion and confirmed by the Takeda physician/designee. The Follow-up Period or the Open-Label Treatment Extension Period consisting of follow-up visits every 4 weeks will start after the end of the Double-Blind Treatment Period (Day 84). The Open-Label Treatment Extension Period will be limited to up to 3 cycles of treatment with ixazomib on the same dose and schedule that they were receiving in the double blind period over an expected duration of 12 weeks

Subjects will receive ixazomib cycles consisting of doses of 0.5 mg (Cohort A), 2 mg (Cohort B), 3 mg (Cohort C), or 4 mg (Cohort D), or placebo. The ascending dose cohorts will be enrolled sequentially. Dosing of subsequent cohorts will not commence until at least 5 subjects in Cohorts A and B and 8 subjects in Cohort C have received at least 1 dose of investigational drug and have reached Day 28 of Cycle 1 or have completed their last evaluation within Cycle 1 with a satisfactory review of all available safety and tolerability data. Subjects discontinued or withdrawn after randomization for nonsafety reasons will only be replaced if the number of subjects per cohort evaluable for safety on Day 28 of Cycle 1 is reduced below 6 subjects for Cohorts C and D, below 5 subjects for lower than 3.0 mg dose cohorts, or the SRC recommends expanding with the same dose to obtain additional information before a dose-escalation decision. Down-titration of ixazomib is permitted for individual subjects for safety and tolerability reasons at any time during the Treatment Period, except for subjects receiving 0.5 mg in Cohort A. If necessary for safety or tolerability reasons or in the judgment of the investigator, ixazomib treatment should be stopped altogether an End of Study Visit should be completed. The subject should then complete the remainder of the study period as the Follow-up Period. Dose modification and dose deferral should be discussed with the Sponsor's Medical Monitor; guidelines for the modification or deferral of doses will be provided.

During the Double-Blind Treatment Period, ixazomib will always be dosed at the study site and

subjects will return to the clinic for each administration of ixazomib. During the Open-Label Treatment Extension Period, subjects will receive the first dose of each cycle at the clinic and the other 2 weekly doses can be given to the subjects to take at home. All subjects will return to the clinic every 4 weeks to receive the first dose of each cycle. For scheduling flexibility, study visits can take place ± 2 days from each scheduled day during the Treatment Period and ± 1 week during the Follow-up Period. A minimum of 120 hours should occur between ixazomib doses. Any variance in the dosing schedule should not alter the schedule of subsequent dosing.

Subjects will undergo safety laboratory assessments, total immunoglobulin G, M, and A (IgG/IgM/IgA), LN assessments including but not limited to UPCR, eGFR, anti-dsDNA antibodies, and complement C3 and C4 levels via a central laboratory according to the schedule in Appendix A. Pharmacogenomic (PGx) and exploratory biomarker samples will also be sent to a central laboratory for analysis.

Ixazomib is an investigational, orally bioavailable 20S proteasome inhibitor with an estimated $t_{1/2}$ of ~ 4 to 9 days in plasma. For Cohorts A to D, plasma concentrations of ixazomib over time will be evaluated following the first dose of Cycle 1 and following the last dose of Cycle 3 of the Double-Blind Treatment Period. Predose samples will be collected before each dose in Cycles 1, 2, and 3 of the Double-Blind Treatment Period. Available PK data will be reviewed as part of the overall safety and tolerability evaluation of ixazomib in LN and for the dose escalation decision.

Recent evidence suggests that genetic variation accounts for differing responses to bortezomib therapy. A single nucleotide polymorphism (SNP) at position 11 in the PSMB1 gene (in the region encoding the leader sequence for the beta subunit of the 20S proteasome) has been associated with reduced proteasome activity and is associated with enhanced bortezomib activity in multiple myeloma and relapsed follicular lymphoma.



In addition, hematology and chemistry safety laboratory assessments will be collected before each dose of ixazomib during the Double-Blind Treatment Period and before each cycle of open-label treatment; the results of all available laboratory tests will be reviewed by the investigator before administration of the scheduled dose of ixazomib. If the central laboratory results are not available for the Open-Label Treatment Extension Period an additional safety laboratory assessment can be conducted at the local laboratory before dosing and they will be recorded in the electronic case report forms (eCRFs). A negative urine pregnancy test result is required before each administration of investigational drug at the visits specified in the schedule of events table.

In common with other immunosuppressant agents, ixazomib may have additional effects on host defense. The subject's immunization status should be reviewed at the Screening Visit, and all appropriate vaccinations should be completed at least 1 month before treatment. These may

include but are not limited to pneumococcal and inactivated influenza vaccines.

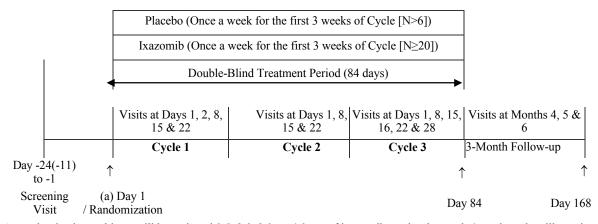
If lymphopenia is noted, subjects may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex viruses, and cytomegalovirus. Antiviral therapy such as acyclovir or valacyclovir may be initiated at the onset of infection after administration of ixazomib. Other antivirals are also acceptable. Provision of medication will be arranged by the investigator from local suppliers and will be reimbursed by the Sponsor.

Each investigator will review any safety findings and laboratory results to determine if a subject should receive the next dose within each cycle. The investigator will evaluate safety and tolerability for each subject on Day -1 and before each dose during every cycle. On Day 22 of each cycle during the Double-Blind Treatment Period, the investigator-led team will evaluate all available safety information for the subject to determine eligibility to initiate the subsequent cycle.

A schematic of the study design is presented below:

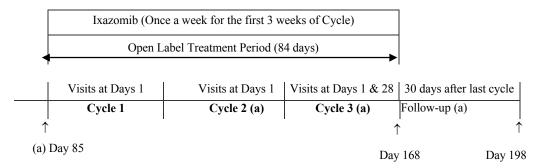
Figure 6.a Schematic of Study Design

Double-Blind Treatment Period



(a) At randomization, subjects will be assigned 0.5, 2.0, 3.0, or 4.0 mg of ixazomib or placebo, each 4-week cycle will consist of 3 once-a-week oral doses. In case abnormal, clinically significant findings are observed upon discharge, subjects may be brought back to the clinic for re-evaluation per investigator's discretion.

Open Label Treatment Period

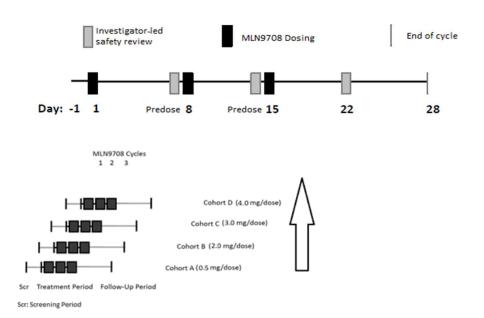


(a) all subjects who enter the open label treatment period will have monthly visit up to at least Day 168. If open-label treatment is terminated before the completion of all 3 cycles, an end of treatment visit will be performed (Day 28 of current cycle) and the subsequent cycle Day 1 visits will be replaced with a follow-up visit.

Dose escalation will be sequential with escalation only considered after all the following conditions have been met (see Section 7.4.2 for dose escalation criteria):

- 1. All subjects in the preceding cohort have been randomized;
- 2. All subjects have received at least 1 dose of investigational drug and have reached Day 28 of Cycle 1 or have completed their last evaluation within cycle 1.
- 3. Before any dose escalation, the SRC (at the minimum consisting of sponsor personnel and principal investigator), will review all the available safety, tolerability and PK data of the entire dose-level cohort to decide if dose escalation is deemed safe.

Figure 6.b Overall Design of the Double-Blind Treatment Period, With Proposed Dose Escalation



6.2 Justification for Study Design, Dose and Endpoints

The primary objective of the study is to characterize the safety and tolerability of ixazomib following multiple oral dose administration in subjects with LN. The study is therefore designed as a double-blind, placebo-controlled study in order to avoid subjective bias in the assessment of the safety and tolerability of ixazomib in this population. The ixazomib doses are 0.5 to 4 mg, dosed orally in three 4-week cycles, each cycle consisting of once-a-week doses given for 3 weeks followed by a 13-day break from the last dose. Subjects who received a dose ≤2.0 mg and completed all cycles including the Follow-up Period, will be permitted to re-enroll into the 2.0 and 3.0 mg dose groups, as appropriate. The dosing schedule is based on the oncology dosing schedule which is currently employed in phase 3 oncology studies.

The justification for the dose range in the proposed study is primarily based on data from the oncology program. The doses of oral ixazomib used in the oncology program range from 0.24 to 3.95 mg/m^2 and fixed doses of 3 to 5.5 mg, as a single agent or in combination with lenalidomide and/or dexamethasone. The starting dose of 0.5 mg is lower than that used in oncology subjects, with only 3 subjects in the oncology program have received an estimated fixed dose of $\sim 1.0 \text{ mg}$.

The top dose in this MRD study in LN of 4 mg is lower than the single-agent MTD of 2.97 mg/m^2 (approximately equivalent to 5.5 mg fixed dose) administered once weekly in subjects with RRMM (study C16004). The dose levels in study C16004 ranged from 0.24 mg/m^2 ($\sim 0.44 \text{ mg}$) to 3.95 mg/m^2 ($\sim 7 \text{ mg}$). The starting dose was 0.24 mg/m^2 , and the escalation

proceeded with doses of 2.0-, 1.67-, 1.50-, 1.40-, and 1.33-fold over the previous dose level thereafter. Three to 6 subjects were evaluated at each dose level during Cycle 1 for predefined DLTs. The actual initial doses administered across these 8 dose levels ranged from 0.2 to 8.9 mg. Three subjects had DLTs; 2 of 4 subjects at 3.95 mg/m² CTCAE Grade 3 nausea, vomiting, and diarrhea and Grade 3 erythema multiforme. The actual initial doses of ixazomib administered to the subjects in the 3.95 mg/m² Cohort were 6.5 to 8.9 mg. At the 2.97 mg/m² dose level, 1 of 6 subjects had DLTs of Grade 3 nausea, vomiting, and diarrhea. All DLTs were reversible and the subjects continued the study at the next lower dose. The actual initial doses of ixazomib administered to the subjects in the 2.97 mg/m² Cohort were 4.4 to 7.2 mg. Overall, the maximum tolerated doses (MTD) determined in the oncology studies ranged between 4 (in combination) and 5.5 mg (as single agent) (Section 4.1.4).

A population pharmacokinetic model was constructed based on the PK data of 4 clinical phase 1 trial in oncology patients (C16001, C16002, C16003, C16004). Using this model it was investigated whether body size covariates (weight or body surface area [BSA]) significantly affect the clearance of ixazomib. Based on this analysis, neither weight nor BSA were significant, therefore the clinical development of ixazomib transitioned from BSA-based dosing to fixed dosing (see the ixazomib IB for further details). The recommended phase 2 and 3 dose of 2.23 mg/m² translated into a fixed dose of 4 mg based on the results from this population PK analysis; thus, all subjects in the phase 2 portion of the C16005 study received a fixed dose of 4 mg weekly. The MTDs of both ixazomib as a single-agent and when combined with lenalidomide and dexamethasone were the same, 2.97 mg/m² (5.5 mg). The current dose of 4 mg (fixed) used for the phase 3 combination studies in oncology for the once weekly schedule is 1 dose level lower than the MTD.

Anticipated human exposures in terms of median AUC_{168} at the planned clinical doses up to 4 mg are lower than the exposures in the dog toxicology study at the NOAEL dose and higher than that observed at the NOAEL dose in the rat toxicology study (Table 6.a). However, although the margins are <1 for the 4 mg dose for both C_{max} and AUC_{168} in rat, the exposures reached at the top dose proposed within this study of 4 mg are still lower than those observed in the dog studies at the NOAEL dose and in the current clinical MTD of 2.97 mg/m² (~5.5 mg). In terms of median AUC_{168} values the predicted exposure at the MTD is 1.87 μ g·hr/mL and the value at the 4 mg dose is 1.35 μ g·hr/mL, therefore, ~1.4-fold lower than the exposure at the MTD (see Table 6.a). The low incidence and mainly mild to moderate severity of AEs that occurred in study C16004 at doses up to ~4 mg (lower than the MTD) suggest that the risk of treatment-related SAEs in the planned MRD over the proposed dose range is likely to be manageable.

For subjects who are re-enrolled in the 2.0 or 3.0 mg dose groups, accumulation of ixazomib in plasma is not expected or will be minimal, as the apparent terminal half-life of ixazomib is approximately 4 to 9 days, the Follow-Up Period following the end of treatment (Day 84) is 3 months (Day 168), which provides a total washout of ixazomib approximately 9 times longer than the upper terminal half-life estimate of 9 days. Before re-enrollment, subjects will be required to undergo screening and to meet the inclusion criteria; therefore, re-enrollment is not expected to be an additional risk to eligible subjects.

Table 6.a Summary of the Simulated Human Exposures Margins Relative to Nonclinical Toxicity Studies and Clinical MTD

MLN9708	Predicted Human Exposure Parameters (a) (95% Prediction Interval)		Estimated Human Exposure Margins (fold)					
Dose (mg)			Rat (b)		Dog (c)		MTD (d)	
	C _{max} ng/mL	AUC ₁₆₈ μg·hr/mL	C_{max}	AUC ₁₆₈	C_{max}	AUC ₁₆₈	Cmax	AUC ₁₆₈
0.5	10.02 (2.90, 35.98)	0.168 (0.058, 0.478)	0.60	2.87	13.6	11.5	11.06	11.10
2	38.67 (12.28, 160.56)	0.644 (0.215, 1.998)	0.15	0.75	3.52	3.01	2.87	2.90
3	56.34 (18.61, 214.25)	0.986 (0.344, 2.872)	0.11	0.49	2.41	1.97	1.97	1.89
4	80.20 (23.12, 288.59)	1.350 (0.425, 4.248)	0.07	0.36	1.70	1.44	1.38	1.38

(a) A population PK model for ixazomib in plasma was developed earlier based on the available PK data of clinical trials in the oncology program [Ixazomib IB version 8, Section 5.4]. Using that model PK parameters were estimated based on data from the oncology trials C16003 and C16004, which resemble most closely the planned MRD trial with respect to the dosing schedule. The model was then used for the simulation of 1000 PK profiles for each dose group of the planned trial in LN. For these profiles individual C_{max} and AUC_{168} values representing the exposure following the final dose in Cycle 3 (Day 15 of Cycle 3) were calculated and their distributions summarized as median and 95% prediction interval.

- (b) Rat exposures (C_{max} and AUC_{168}) at the NOAEL (0.2 mg/kg/dose) are from study WIL-416165. The mean (Day 168) Cmax and AUC_{168} values are 5.99 ng/mL and 482 ng·hr/mL, respectively (mean of both sexes).
- (c) Dog exposures (Cmax and AUC[0-168]) at the NOAEL (0.10 mg/kg/dose) from study WIL-416164. The mean (Day 252) C_{max} and AUC₁₆₈ values are 136 ng/mL and 1940 ng·hr/mL, respectively, (mean of both sexes).
- (d) Estimates were based on population-based clinical exposure at the MTD (5.5 mg) in Study C16004. The derived Cmax and AUC_{168} are 110.83 ng/mL and 1.87 µg·hr/mL, respectively, (Day 15 Cycle 3).

In conclusion, the safety of ixazomib is supported by clinical experience gained from the ongoing oncology program. As of 27 March 2017, data are available from 941 patients known to have received at least 1 dose of either the IV or oral ixazomib formulations across the oncology clinical development program; in addition, 2682 patients have been enrolled in phase 3 clinical studies in RRMM, newly diagnosed MM and RRAL. The emerging safety profile indicates that ixazomib administration can lead to AEs that are generally manageable and reversible with dose reduction and supportive care. Additionally, the AEs in the combination studies are consistent with the safety profile of the individual agents in the combination regimen (eg, myelosuppression is common in regimens containing melphalan, and rash is common in regimens containing lenalidomide). While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention.

Differences in the PK of ixazomib between oncology and LN subjects are expected to be minimal. In terms of demographic parameters the main differences between the 2 populations are age and renal function, which are anticipated to have only a minimal impact on systemic exposure. Participants in this study will be closely monitored, with once-a-week clinic visits during the Double-Blind Treatment Period, at least monthly visits at the Open-Label Treatment Extension Period and additional clinical assessment/interventions as needed. Overall the risk to LN subjects is expected to be minimal.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/ independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before first dose of study drug on Day 1.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

- 1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
- 2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written informed consent form and any required privacy authorization before the initiation of any study procedures.
- 3. The subject is female or male and aged 18 to 75 years, inclusive.
- 4. Subject has a diagnosis of SLE defined by meeting either the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria or the ACR criteria for the classification of SLE. The 4 criteria required by ACR classification are not required to be present at Screening for eligibility (see Appendix H).
- 5. The subject has a definite diagnosis of LN based on a kidney biopsy done within 2 years of the Screening Visit which demonstrated ISN/RPS Class III, IV or V changes [excluding Class III (C), IV-S (C) and IV-G (C)] or WHO 1982 classification Class III, IV or V (excluding Class IIIc and IVd)(see Appendix I).
 - a) If no biopsy was done within 2 years of Screening Visit, biopsy can be done during the screening period as a study procedure.
 - b) Co-existence of classes is permitted.
 - c) Subjects with a confirmed diagnosis of LN who have not had a renal biopsy within 2 years of screening and cannot have a renal biopsy during the screening, may be eligible for the study if they have proteinuria of ≥1 g/24 hours due to a LN renal flare occurring within 1 year of the screening. A LN renal flare is defined as at least a doubling of proteinuria with no other explanation such as a secondary pathology (eg, diabetic nephropathy) or change in medication (eg, reduction of angiotensin-converting enzyme /angiotensin II receptor blocker).
- 6. The subject has a renal biopsy demonstrating either ISN/RPS or WHO Class V or Class V with Class 2 nephritis with a UPCR of ≥1 or the subject has a renal biopsy demonstrating either active ISN/RPS or WHO Class III or IV nephritis, defined by either one of the following criteria:
 - a) A UPCR* of ≥1.0 at Screening

OR

- b) A UPCR* >0.5 at Screening and at least one of the following:
 - i. Active urine sediment in the absence of infection or other cause within 3 months of screening, defined as at least one of the following:
 - ≥5 red blood cells (RBC) per high power field, not due to causes other than LN.
 - ≥5 white blood cells (WBC) per high power field in the absence of infection.
 - Presence of cellular casts.
 - ii. The subject has increased levels (above upper limit of normal [ULN] serum dsDNA autoantibodies at screening.
 - iii. Low complement (either C3 or C4) at Screening (≥25% lower than the lower limit of normal [LLN]).
 - iv. Biopsy within 3 months before screening visit indicating active proliferative lupus glomerulonephritis ISN/RPS class III or IV changes [excluding Class III (C), IV-S (C) and IV-G (C)] or WHO 1982 classification Class III or IV (excluding Class IIIc and IVd), with co-existing Class V permitted.
 - *Subjects may be re-screened once for urinary sediment, proteinuria or complement levels within 2 weeks of the original screening visit.
 - * UPCR value for eligibility will be based on the average UPCR obtained from the 3 specimens collected during screening.
- 7. The subject has had an inadequate response, in the judgment of the investigator, to at least 3 months of an immunosuppressive regimen including single or sequential use of at least one of the following: CYC, mycophenolate mofetil (MMF), mycophenolic acid (MA) or AZA.
- 8. If the subject is on glucocorticosteroids, must be on stable dose equivalent to 20 mg/day or less of prednisone for at least 2 weeks before the first dose of study medication. Subjects who are on a stable dose equivalent to >20 mg/day and ≤30 mg/day of prednisone may be allowed to the study reviewed by the adjudication committee and approved by the medical monitor; however, the steroid dose should be tapered as specified in Section 8.1.1.3.
- 9. Male subjects who are sexually active with women of child bearing potential, even if surgically sterilized (ie, status post-vasectomy), must:
 - a) Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug.
- 10. Female subjects who are of child bearing potential must:
 - a) Agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study.
- 11. This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized) and subjects who received a dose

- ≤2.0 mg and have completed all cycles including the Follow-up Period. If re-enrolled, the subject must be re-consented.
- * The re-enrollment of all subjects who received a dose ≤2.0 mg and completed all cycles including the Follow-up Period is permitted to Cohort B and C (2.0 mg and 3.0 mg dose cohorts) after completion of all cycles including the follow-up period if they had no drug-related AEs greater than Grade 1 which required study drug dose modification, no AEs greater than Grade 2, continue to meet all inclusion and exclusion criteria, and the SRC has reviewed and approved enrollment of the subject into a higher dose cohort.
- 12. Subjects must be receiving Standard of Care treatment with an immunosuppressant drug for the treatment of LN (eg, mycophenolate mofetil, mycophenolic acid or azathioprine, see Section 8.1.1.2).

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

- 1. The subject has received any investigational compound within 30 days or 5 half-lives, whichever is the longer, before Screening or is currently participating in another interventional clinical study.
- 2. The subject has received ixazomib, bortezomib, or another proteasome inhibitor in a previous clinical study or as a therapeutic agent.
- 3. The subject is a sponsor employee, an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg. spouse, parent, child, sibling), or may consent under duress.
- 4. The subject has an autoimmune disease other than SLE as their main diagnosis.
- 5. The subject has drug-induced SLE.
- 6. The subject has severe, active central nervous system lupus (BILAG A or B).
- 7. The subject has an eGFR of <30 mL/min/1.73m², or is on dialysis, or is expected to have a renal transplant within 1 year of randomization, or has had a renal transplant.
- 8. The subject has a severe acute infectious disease (eg, untreated active tuberculosis (TB), acute viral hepatitis, human immunodeficiency virus), untreated latent tuberculosis (TB), or infections requiring IV anti-microbial treatment within 2 months preceding the Screening Visit.
- 9. The subject has a history of a malignant disease (except successfully treated basal cell carcinoma, squamous cell carcinoma, or cervical carcinoma in situ) within 5 years before Screening.
- 10. The subject has one of the following laboratory test values:

- a) IgG <75% of LLN. If low IgG is due to significant proteinuria due to LN activity, subjects with IgG >4.2 g/dL can be included. The cause of low IgG must be due to LN proteinuria and all other causes of hypo-gammaglobulinemia must be ruled out.
- b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the central laboratory's ULN.
- c) Bilirubin >1.5 x ULN (Note: subjects with Gilbert Syndrome with a confirmed diagnosis and documented in the subject's medical record will not be excluded based on this criterion).
- d) Platelets < 75,000/mm³.
- e) Neutrophils <1500/ mm³.
- f) Hemoglobin <8 g/dL.
- g) Positive for Hepatitis B Surface Antigen.
- h) Positive for Hepatitis C antibody.
- 11. The subject has a history of drug or alcohol abuse or dependence (as defined by Diagnostic and Statistical Manual of Mental Disorders, fourth Edition [DSM-IV]) within 1 year before screening visit (see Appendix J).
- 12. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 3 months after participating in this study; or intending to donate ova during such time period.
- 13. If male, the subject intends to donate sperm during the course of this study or for 90 days after the last dose. Male subjects planning to father during clinical trial conduct or within 90 days after the last planned dose of trial treatment.
- 14. The subject has moderate or severe liver disease (Child-Pugh B or C), and/or positive serological tests for hepatitis B (other than due to prior immunization) or hepatitis C.
- 15. The subject is taking excluded medications (Section 7.3).
- 16. The subject has a history of clinically significant neuropathies of National Cancer Institute CTCAE v 4.03 Grade 2 or higher.
- 17. The subject has been treated with cyclophosphamide within 4 weeks of the Screening Visit.
- 18. The subject has been treated with >3 g/day of mycophenolate mofetil within 4 weeks of the Screening Visit.
- 19. The subject has been treated with belimumab, abatacept, or tocilizumab within 3 months of the Screening Visit.
- 20. The subject has been treated with epratuzumab, alemtuzumab, rituximab or other cell depleting biological agents within 6 months of the Screening Visit.

21. Current symptoms of severe, progressive, or uncontrolled non-SLE related renal, hepatic, hematological, gastrointestinal (including hypomotility and ulcerative/inflammatory conditions), pulmonary, cardiac, neurological, or cerebral disease, or other concomitant medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.

7.3 Excluded and Restricted Medications, Procedures and Dietary Products

Subjects should remain on their current stable and allowed therapies during the screening period and throughout the duration of the study. Initiation of therapy with any of the following medications or treatments after randomization (Study Day 1) is not allowed (see Table 7.a):

Angiotensin converting enzyme inhibitors, angiotensin II receptor blocking agents

Methotrexate, Leflunomide

Azathioprine

Calcineurin inhibitors (cyclosporine, tacrolimus, etc)

Cyclophosphamide

mTOR inhibitors (sirolimus or everolimus)

Belimumab, Rituximab or any other biologic agents for the treatment of lupus

Thalidomide

Gold compounds

Experimental therapies for the treatment of SLE

Intravenous immunoglobulin

Plasmapheresis, Lymphopheresis, Prosorba column

Dialysis

The prescribing label of all concomitant medications used as concomitant therapy should be evaluated by the investigator for continued administration during the study for known toxicities, DDIs, or any anticipated risks associated with co-administration with the investigational drug ixazomib.

Restrictions on use or starting of certain medications during the duration of the study are specified in Table 7.a (prescription or nonprescription).

Table 7.a Prohibited Medications

28 days before Day 1 and during the study	1 14 days before Day 1	Starting Treatment after Day 1 and during the study
Cyclophosphamide	Nutraceuticals (eg, St. John's wort)	Angiotensin converting enzyme inhibitors, angiotensin II receptor blocking agents
		Methotrexate, Leflunomide
		Azathioprine
		Calcineurin inhibitors (cyclosporine, tacrolimus, etc)
		mTOR inhibitors (sirolimus or everolimus)
		Belimumab, Rituximab or any other biologic agents for the treatment of lupus
		Thalidomide, Gold compounds
		Experimental therapies for the treatment of SLE
		Intravenous immunoglobulin
		Plasmapheresis, Lymphapheresis, Prosorba column
		Dialysis
Influenza vaccines or immunization with a live vaccine		
	Clinically significant CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital	Clinically significant CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

Systemic treatment with any of the metabolizing enzyme inducers listed in Table 7.a is not permitted in this study given the risk of DDI with an inducer and the potential decrease in ixazomib exposure.

All necessary supportive care consistent with optimal patient care shall be available to subjects as necessary.

The prescribing label of all concomitant medications used as concomitant therapy should be evaluated by the investigator for continued administration during the study for known toxicities, DDIs, or any anticipated risks associated with coadministration with the investigational drug ixazomib. During participation in the study, subjects must be instructed not to take any medications, including over-the-counter medications, without first consulting the investigator.

7.4 Diet, Fluid, and Activity Control

Subjects should be encouraged to drink at least 1.5 liter of fluids a day, especially on days requiring fasting (for characterization of glucose responses, as per protocol). Particular attention should be given to adequate fluid intake in case of gastrointestinal toxicities (eg, vomiting, diarrhea, loss of appetite) to avoid dehydration.

7.4.1 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.19.

- 1. Pretreatment event or AE. The subject has experienced a pretreatment event or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pretreatment event or AE.
 - Liver Function Test Abnormalities

Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.10), if the following circumstances occur at any time during study medication treatment:

- ALT or AST >8 × ULN, or
- ALT or AST >5 × ULN and persists for more than 2 weeks, or
- ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio >1.5, or ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
- If ALT or AST >3 ×ULN, but <5XULN, laboratory tests should be repeated until recovery of observed (see Table 7.d) and ixazomib withheld. Upon recovery, ixazomib may be resumed at lower dose. If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, and this observation cannot be explained by concomitant disease or another alternative etiology, the investigator should contact the Medical Monitor for considerate on permanent discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies.
- 2. Major protocol deviation. The discovery after administration of the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
- 3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
- 4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should <u>not</u> be recorded in the "voluntary withdrawal" category).

- 5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
- 6. Pregnancy. The subject is found to be pregnant.
 - Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.12.
- 7. Initiation of therapy with a recombinant granulocyte colony stimulating factor (G-CSF), including filgrastim or lenograstim, or intravenous immunoglobulin (IVIG).
- 8 Other

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.4.2 Dose Escalation Criteria

All decisions concerning dose escalation will be made by Takeda (at a minimum, the clinical science representative(s) and pharmacovigilance physician) and the principal investigator. The following dose escalation is planned outlined in Table 7.b.

Table 7.b Dose Increase Factors

Dose (mg)	Dose Increase Factor
0.5	(starting)
2.0	4.00
3.0	1.5
4.0	1.33

During the Double-Blind Treatment Period, safety labs will be performed at each dosing day, as well as Day 22 of each cycle. The PK will be assessed following the first dose of Cycle 1 and the last dose of Cycle 3.

For each dose level Cohort, the SRC will carefully review the available safety, tolerability, and PK data and determine whether dosing should be escalated in the next Cohort, or lowered or expanded with same dose to obtain additional information before dose-escalation decision or stopped. Additionally, based upon review of available data, unblinding may be considered if deemed critical by the sponsor and investigator(s) to make a decision regarding the conduct of the study or for subject safety. Safety review will include all available AEs, vital signs, ECGs, and laboratory parameters, as well as available PK data.

Dose escalation will depend upon the safety clinical profile of the doses up to and including the preceding dose group and it will not occur until the following conditions are met:

1. All subjects randomized in the preceding dose Cohort, have received at least one dose of study medication (except in case of pre-treatment dropouts) and have reached Day 28 of Cycle 1 or have completed their last evaluation within Cycle 1;

2. Safety (including report of TEAEs, clinical laboratory results and vital signs) and tolerability data of all subjects of the preceding Cohort are reviewed by a SRC and deemed safe to proceed with dose escalation.

Subjects discontinued or withdrawn after randomization for non-safety reasons will only be replaced if the number of subjects per Cohort evaluable for safety on Day 28 of Cycle 1 is reduced below 6 subjects.

All TEAEs reported during the Treatment Period, both within and across cohorts, up to the time of discharge, will be evaluated to assess the need for subject and/or study termination in accordance with the pre-specified criteria for discontinuation/termination.

Following assessment of the TEAE data and predefined criteria for study termination, dose escalation may be interrupted/stopped and the blind broken for further analysis. Based on review of unblinded data, Takeda in consultation with the principal investigator(s) will decide whether and how it is appropriate for the study to proceed.

Within each dose level, if at least 2 subjects develop a DLT, the subjects will be unblinded for any dose-escalation joint safety review meeting. If both subjects are on ixazomib, no further dose escalation beyond that dose will be allowed. If at least 2 subjects develop a DLT leading to discontinuation of ixazomib, then the subjects will be immediately unblinded and if both subjects are on ixazomib, no further dosing will occur in that dose Cohort.

Although DLTs may occur at any point during treatment, primarily the DLTs occurring during Cycle 1 of treatment will be used to make a decision regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels.

7.4.3 DLTs, Dose Modifications, and Stopping Rules

DLT is defined as any of the following TEAEs that occur after a subject has received blinded study medication and that do not have a clear alternate causality (Grades are CTCAE v 4.03):

- 1. Grade 3 or greater neutropenia (absolute neutrophil count [ANC] <1000/mm³), confirmed by repeat test.
- 2. Grade 3 or greater thrombocytopenia (platelets <50,000/mm³), confirmed by repeat test.
- 3. Grade 2 peripheral neuropathy with pain or Grade 3 or greater peripheral neuropathy.
- 4. Grade 3 or greater nausea, emesis, or diarrhea.
- 5. Serious infections defined as infections requiring hospitalization or IV antibiotics (more than 1 dose), systemic antifungal or antiviral intervention.
- 6. ECG with QT interval with Fridericia correction method (QTcF) >500 msec confirmed by repeat ECG.
- 7. Any other Grade 3 or greater nonhematologic toxicity with the following exceptions: Grade 3 arthralgia/myalgia.
 - Brief (<1 week) Grade 3 fatigue.

- 8. A delay of more than 2 weeks in the initiation of Cycles 2 or 3 of treatment because of a lack of adequate recovery of hematological or nonhematologic toxicities.
- 9. A Grade 2 or greater toxicity that requires discontinuation of therapy with ixazomib.

If an individual subject meets the DLT criteria, then specific rules outlined on Table 7.c and Table 7.d will be applied depending on the toxicity.

Table 7.c Monitoring of Hematologic Toxicities and Dose Modification/Drug Stopping Rules

Kules			
Toxicity	Repeat Laboratory Test	Ixazomib	
Neutropenia			
<1,500/mm ³ (1.5 x 10 ⁹ /L)	Repeat test as appropriate based on investigator's clinical judgment	No change	
<1000/mm ³ (1.0 x 10 ⁹ /L)	Repeat test within 72 hours and then repeat test at least $2\times$ a week until neutrophil counts are $\geq 1,000/\text{mm}^3$. Then, repeat test as appropriate based on investigator's clinical judgment.	counts are >1,500/mm³. Upon recovery, ixazomib may be resumed at lower dose. If neutropenia is accompanied by fever ≥38.5°C or infection, then discontinue ixazomib.	
<500/mm ³ (0.5 x 10 ⁹ /L)	Repeat test within 72 hours and then repeat test at least $3 \times a$ week until neutrophil counts are $\geq 1,000/\text{mm}^3$. Then, repeat test as appropriate based on investigator's clinical judgment.	Discontinue ixazomib permanently. Subjects who require treatment with Filgrastim G-CSF (filgrastim, lenograstim or similar) should be discontinued from the study.	
Thrombocytopenia			
<75,000/mm ³ (75 x 10 ⁹ /L)	Repeat test as appropriate based on investigator's clinical judgment	No change	
<50,000/mm ³ (50 x 10 ⁹ /L)	Repeat test within 72 hours and then repeat test at least $2 \times$ a week until platelet counts are $\geq 50,000/\text{mm}^3$. Then, repeat test as appropriate based on investigator's clinical judgment.	Withhold ixazomib until platelet counts are >75,000/mm ³ . Upon recovery, ixazomib may be resumed at lower dose. If thrombocytopenia recurs or is accompanied by clinically significant bleeding, then discontinue ixazomib.	
<25,000/mm ³ (25 x 10 ⁹ /L)	Repeat test within 72 hours and then repeat test at least $3\times$ a week until platelet counts are $\geq 50,000/\text{mm}^3$. Then, repeat test as appropriate based on investigator's clinical judgment.	Discontinue ixazomib permanently.	
Other Hematologic To	xicities		
Grade 3 (severe) hematologic toxicities	Repeat test within 72 hours and then repeat test at least 2× a week until recovery to Grade 2 is observed. Then, repeat test as appropriate based or investigator's clinical judgment.	≤Grade 1.	
Grade 4 (very severe) hematologic toxicities	Repeat test within 72 hours and then repeat test at least 3× a week until recovery to Grade 2 is observed. Then, repeat test as appropriate based or investigator's clinical judgment.		

Table 7.d Monitoring of Non-Hematologic Toxicities and Dose Modification/Drug Stopping Rules

Toxicity	Repeat Laboratory Test	Ixazomib
Severe Cutaneous Skin		Discontinue ixazomib permanently.
Reactions		
Stevens-Johnson Syndrome,		
Toxic Epidermal Necrolysis,		
drug reaction with eosinophilia		
and systemic symptoms (DRESS	S	
syndrome) or pemphigus		
vulgaris		
Infections		
Serious infection requiring		Discontinue ixazomib permanently.
hospitalization, IV antibiotics		
(more than 1 dose), systemic		
antifungal or antiviral		
intervention		
Peripheral Neuropathy		
Newly developed Grade 1		Reduce dose of ixazomib to the
peripheral neuropathy with pain		previous dose level, except for the 0.5
or Grade 2 peripheral neuropath	y	mg cohort.
Grade 2 peripheral neuropathy		Withhold ixazomib until toxicity is
with pain or Grade 3 peripheral		≤Grade 1
neuropathy		Upon recovery, ixazomib may be
		resumed at lower dose except for the 0.5
Grade 4 peripheral neuropathy		mg cohort.
Other AEs considered related	to incremit	Discontinue ixazomib permanently.
ECG with QTcF >500 msec	Repeat ECG within the same day of	Discontinue ixazomib immediately.
confirmed by repeat ECG	initial finding.	Discontinue ixazonno ininiediatery.
Decrease in eGFR >25% from	Repeat test within 72 hours from initial	Discontinue ixazomib immediately.
Baseline or doubling of serum	finding.	Discontinue ixazonno ininiediatery.
creatinine from Baseline	inding.	
IgG <50% of LLN	Repeat test within 72 hours from initial	Discontinue ixazomib immediately.
IgO \3070 OI LLN	finding.	Subjects who require treatment with
	inding.	IVIg should be discontinued from the
		study.
Grade 3 toxicities	If applicable, repeat test within 72 hours	Withhold ixazomib until toxicity is
Grade 5 toxicities	and then repeat test 2× a week until	≤Grade 1 or returned to the subject's
	recovery to Grade 2 is observed.	baseline condition.
	Thereafter, repeat test as appropriate	Upon recovery, ixazomib may be
	based on investigator's clinical judgment.	
	based on investigator's eninear judgment.	mg cohort.
Grade 4 toxicities	If applicable, repeat test within 72 hours	Discontinue ixazomib permanently.
Grade 4 toxicities	and then repeat test 3× a week until	Discontinue ixuzonno permanentry.
	recovery to Grade 2 is observed.	
	Thereafter, repeat test as appropriate	
	based on investigator's clinical judgment.	
	out of investigator beninear judgment.	

The blinded treatment cycles with ixazomib will be repeated every 28 days for a total of 3 cycles. Subjects can also receive up to 3 additional cycles of open label treatment with ixazomib at the discretion of investigator. For a new cycle of treatment to begin, the subject's absolute neutrophil count must be $\geq 1,500 \text{ mm}^3$ and the platelet count must be $\geq 75,000 \text{ mm}^3$. In addition, all other toxicities considered to be related to treatment with ixazomib must have resolved to \leq Grade 1 or to the subject's baseline values before a new cycle of treatment may begin.

If the subject fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that time, the subject should be re-evaluated to determine whether the criteria for retreatment have been met. If a delay in the initiation of the next cycle of more than 2 weeks is required because of incomplete recovery from treatment-related toxicity, then this event will be considered a DLT. If toxicity does not resolve by 2 weeks, then the subject should be considered for removal from the study. This decision will be made in the context of emerging clinical data about our understanding of ixazomib in subjects with LN and in consultation with the investigators and Takeda medical monitor and pharmacovigilance physician. If, in the opinion of the investigator and the Takeda physicians, it is in the subject's best interest to continue treatment with ixazomib, then ixazomib will only be resumed after recovery from the toxicity or toxicities in question to ≤Grade 1 or to baseline values and the dose of ixazomib should be reduced by at least 1 dose level.

Similarly, if dosing with ixazomib needs to be withheld within a given cycle because of toxicity, then ixazomib will only be resumed after recovery of the toxicity or toxicities in question to \leq Grade 1 (if a laboratory parameter, recovery should be confirmed by repeat test) and the dose of ixazomib should be reduced by at least 1 dose level. When a dose reduction of ixazomib is required, no re-escalation of dose will be permitted for that subject. For the first Cohort (0.5 mg dose), no reduction will be made. If the DLT recurs upon resuming ixazomib at a lower dose, then ixazomib should be immediately discontinued.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may terminate a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4.1. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the Final Visit/Early Termination (ET).

Subjects discontinued or withdrawn after randomization for nonsafety reasons will only be replaced if the number of subjects per cohort evaluable for safety on Day 28 of Cycle 1 is reduced below 6 subjects for Cohorts C and D, below 5 subjects for lower than 3.0 mg dose cohorts, or the SRC recommends expanding with the same dose to obtain additional information before a dose-escalation decision.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Investigational Drug

Double-Blind Treatment Period

In the Double-Blind Treatment Period of protocol, the term study medication refers to all or any of the drugs defined below:

- MLN9708 (ixazomib) capsules 0.5 mg (as boronic acid) and matching placebo in dark green size 3 capsules.
- MLN9708 (ixazomib) capsules 2 mg (as boronic acid) and matching placebo in Swedish orange size 2 capsules.

The active capsule strengths contain both drug substance and inactive ingredients. The corresponding placebo capsules contain all of the same components of active MLN9708 (ixazomib) with the exception of the active ingredient, which is substituted with an equivalent amount of Mannitol. The manufacturer of MLN9708 (ixazomib) is Haupt Pharma Amareg GmbH Germany. The investigational drug will be packaged in foil/foil blistered child resistant wallets as weekly doses administered on Days 1, 8 and 15 of each cycle. Each wallet of MLN9708 (ixazomib) active or placebo will bear a single-panel label or booklet that includes pertinent study information, medication ID numbers for interactive voice response system/interactive web response system (IVRS/IWRS) dispensing purposes and local regulatory requirements. Wallets will contain either 1, 2, or 3 capsules based on dose required. See Table 8 a.

Open-Label Treatment Extension

In the Open-Label Treatment Extension of this protocol, the term study medication refers to all or any of the drugs defined below:

- MLN9708 (ixazomib) capsules 2 mg (as boronic acid) in Swedish orange size 2 capsules.
- MLN9708 (ixazomib) capsules 3 mg (as boronic acid) in light grey size 4 capsules.
- MLN9708 (ixazomib) capsules 4 mg (as boronic acid) in ivory size 3 capsules.

The manufacturer of MLN9708 (ixazomib) is Haupt Pharma Amareg GmbH Germany. The investigational drug will be packaged in foil/foil blistered child resistant wallets as monthly doses administered on Days 1, 8, and 15 of each cycle. Each wallet of MLN9708 (ixazomib) will bear a single-panel label or booklet that includes pertinent study information, medication ID

numbers for IVRS/IWRS dispensing purposes and local regulatory requirements. Wallets will contain 3 capsules (see Table 8.a).

8.1.1.2 Concomitant Medications for Treatment of SLE While on Study Medication

<u>Corticosteroids</u>

If receiving corticosteroids, subjects should remain on their stable screening dose at least until completion of dosing with investigational drug in the first cycle on Day 15, when tapering the dose of corticosteroid, can start as specified in Section 8.1.1.3. Temporary increases in the dose of corticosteroids are allowed as a rescue therapy (see Section 8.1.1.3).

<u>Immunosuppressants</u>

Subjects should remain on their stable dose of immunosuppressive therapies throughout the study and consistent with labeling recommendations. On the days of dosing with ixazomib, subjects should skip their immunosuppressant medication. On the next day, regular dosing with the immunosuppressant agent should be resumed.

Decreases in the dose of immunosuppressants are allowed at the discretion of the investigator due to toxicity. Increase in the dose of immunosuppressants is allowed after completion of the last cycle with ixazomib (or 2 weeks after last dose). The concomitant use of cyclophosphamide is not allowed during the study.

Anti-proteinuric agents

Subjects with active LN and significant proteinuria should receive anti-proteinuric agents, such as angiotensin II receptor blockers, angiotensin-convertase enzyme inhibitors or any combination of these drugs, unless contraindicated, not tolerated, previously demonstrated to be not effective, or not consistent with local standard of care.

Subjects should have started treatment with anti-proteinuric agents before randomization and the dose should remain stable throughout the treatment period of the study and doses should not be increased. Reduction in the dose of anti-proteinuric agents is allowed for tolerability or toxicity reasons.

Use of other antihypertensives medications (eg, calcium channel blocking agents) is permitted for blood pressure control as needed.

Anti-malarials and topical therapies

Chloroquine, hydroxychloroquine, quinacrine should be continued at stable doses and their safety monitored using standard and accepted monitoring regimens. Topical therapies (including eye, ear, nose treatments) may be continued and their use modified as indicated.

Nonsteroidal Anti-inflammatory Drug

Nonsteroidal anti-inflammatory drugs (NSAIDs) (including aspirin/acetylsalicylic acid) use is not prohibited, although their use is generally discouraged in the setting of active renal disease.

Other medications

Use of concomitant medications used by the subject for treatment of diseases or symptoms not related to SLE is permitted during the study, unless the medication is prohibited. Use of vitamins is permitted throughout the study. For a list of restricted or prohibited medications, see Section 7.3.

8.1.1.3 Corticosteroids Taper and Rescue Therapy

<u>Corticosteroids (Prednisone or Prednisone Equivalent) Taper After Randomization</u>

Subjects Taking Glucocorticosteroids Equivalent to ≤ 20 mg of Prednisone at Baseline:

After completion of dosing in the first cycle, a decision on tapering the corticosteroid dose can be made at the discretion of the investigator. To start tapering the corticosteroid, a subject must meet all of the following criteria:

- 1. UPCR: no more than 25% above the greater of the values at the Screening or Randomization (Study Day 1) visit.
- 2. eGFR: no more than 15% worse than the lesser of the values at Screening or Day 1 Visit.
- 3. No clinically significant increase activity of the urine sediment, as determined by the investigator.
- 4. No clinically significant progressive active extra-renal lupus as determined by the investigator.

Tapering the corticosteroid should be initiated in the next visit and the proposed goal is to achieve \geq 50% reduction in the dose of corticosteroid by the end of the next cycle with ixazomib (around week 8 in the study). Further tapering can continue during the last cycle with ixazomib at the discretion of the investigator.

If a subject is unable to initiate taper of corticosteroids during the study AND the investigator determines that a medication not allowed in the protocol is needed to treat the renal or non-renal manifestations of SLE, the subject must be discontinued from treatment with study drug.

Subjects Taking Glucocorticosteroids Equivalent to >20 mg to \le 30 mg of Prednisone at Baseline:

The investigator should attempt to taper subjects' steroid dose to \leq 25 mg/day prednisone after Day 15 of Cycle 1 (Week 4) and to \leq 20 mg after Day 15 of Cycle 2 (Week 8) of treatment considering the aforementioned criteria.

Rescue Therapy With Corticosteroids

If, in the judgment of the investigator, there is need for increase in corticosteroid dosage during the first or second cycles, the dosage may be increased to a dose that is less than or equal to 0.5 mg/kg/day or 40 mg/day, whichever is lower. However, dose should be tapered to the pre-flare level or 10 mg/day, whichever is greater, within 4 weeks or less. If tapering is not possible

AND the investigator determines that a medication not allowed in the protocol is needed to treat the renal or non-renal manifestations of SLE, the subject must be discontinued from treatment with study drug.

Subjects who require increase in corticosteroid dose above 0.5 mg/kg/day or 40 mg/day of prednisone or equivalent for control of LN activity or control a flare of non-renal lupus activity during the study will be discontinued from study drug.

8.1.2 Storage

All clinical trial material must be kept in an appropriate, limited-access, secure location until it is used or returned to the sponsor or designee for destruction. All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day. See pharmacy manual for specific receipt instructions, temperature excursion notification process, and capsule handling instructions.

Recent stability testing has expanded the permitted ixazomib/placebo temperature range. All new ixazomib/placebo capsules batches will be labeled with the expanded range: *Do not store above* 25°C/Do not freeze or *Do not store above* 30°C/Do not freeze. Earlier batches of ixazomib/placebo capsules (labeled with the initial storage range: *Store at* 2°C to 8°C/36°F to 46°F) remain acceptable for use until expired. Sites may receive ixazomib/placebo capsules with new or initial labeling as supplies are transitioned. In either case, sites must store ixazomib/placebo as directed on the label. The investigator should ensure that study medication is used only in accordance with the approved protocol. Study medication will be dispensed only for subjects enrolled in the study.

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct each subject to swallow ixazomib/placebo capsules whole with water and not to break, chew or open the capsules. Study drug should be taken on an empty stomach, at least one hour before or no sooner than two hours after a meal. Each capsule should be swallowed with a sip of water. A total of approximately 240 mL of water should be taken with the capsules.

During the Double-Blind Treatment period, all dosing will occur while subjects are in the clinic under the supervision of the principal investigator or designee as indicated in Table 8.a. During the Open-Label Treatment Extension, the first dose of each cycle will occur while subjects are in the clinic, and the remaining doses will be self-administered at home.

Table 8.a Treatment Groups

Cohort	Treatment Group	Active Dose (N=6)	Placebo Dose (N=2)
A	MLN9708 (ixazomib) 0.5 mg (as boronic acid) or matching placebo		One Placebo for MLN9708 (ixazomib) 0.5 mg (as boronic acid) dark green size 3 capsules
В	MLN9708 (ixazomib) 2 mg (as boronic acid) or matching placebo	One MLN9708 (ixazomib) 2 mg (as boronic acid) Swedish orange size 2 capsule	One Placebo for MLN9708 (ixazomib) 2 mg (as boronic acid) Swedish orange size 2 capsule
C	MLN9708 (ixazomib) 3 mg (as boronic acid) or matching placebo	(as boronic acid) Swedish orange size 2 capsule	One Placebo for MLN9708 (ixazomib) 2 mg Swedish orange size 2 capsule and
		and Two MLN9708 (ixazomib) 0.5 mg (as boronic acid) dark green size 3 capsules	Two Placebo for MLN9708 (ixazomib) 0.5 mg (as boronic acid) dark green size 3 capsules
D	MLN9708 (ixazomib) 4 mg (as boronic acid) or matching placebo	Two MLN9708 (ixazomib) 2 mg (as boronic acid) Swedish orange size 2 capsules	Two Placebo for MLN9708 (ixazomib) 2. mg (as boronic acid) Swedish orange size 2 capsules
OLE		MLN9708 (ixazomib) 2 mg (as boronic acid) capsules in Swedish orange size 2 capsules MLN9708 (ixazomib) 3 mg (as boronic acid) capsules in light grey size 4 capsules MLN9708 (ixazomib) 4 mg (as boronic acid) capsules in ivory size 3 capsules	

OLE=Open-Label Treatment Extension Period

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. If overdose occurs, consider close observation including hospitalization for hemodynamic support. Gastric lavage may be considered if instituted within 1 hour of ingestion of ixazomib overdose.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

SAEs of overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, consider close observation including hospitalization for hemodynamic support (see Section 10.1.5).

8.2 Study Medication Assignment and Dispensing Procedures

The investigator or the investigator's designee will use the IVRS/IWRS to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number. The medication identification (MED ID) number of the investigational drug to be dispensed will then be provided by the IVRS/IWRS. If the sponsor supplied drug for Cohorts A to D is lost or damaged, the site can request a replacement from the IVRS/IWRS. The randomization sequence number will be entered onto the eCRF. At subsequent drug dispensation visits, the investigator or designee will again contact the IVRS/IWRS to request additional investigational drug for a subject.

For each Dosing Cohort, randomized subjects will be assigned a 4-digit randomization sequence number in the order which they are enrolled. Randomization sequence numbers will start from X001 based on cohort assignment. For example, the randomization sequence numbers will start from 1001 for Cohort A and 2001 for Cohort B, etc. Additional randomization numbers will be generated to accommodate the replaced subjects. The replacement subject will receive the same treatment as the subject being replaced.

This randomization sequence number will be used by the clinical site to facilitate the pre labeling of PK samples, and will be the only subject identifier used on all sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results. This 4-digit number should only be used for the purposes described in this section. It does not replace the 3-digit subject number which is assigned at the time the informed consent is obtained and which is used for all other procedures to identify the subjects throughout the study.

8.3 Randomization Code Creation and Storage

IVRS/IWRS will generate and maintain the randomization and medication schedules. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through IVRS/IWRS.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational blind is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the sponsor's medical monitor or designee should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents.

For unblinding a subject, the investigational drug blind can be obtained by accessing the IVRS/IWRS.

8.6 Accountability and Destruction of All Study Medication

Drug supplies will be counted and reconciled at the site before being returned to Takeda or designee or being destroyed by the site.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study drug, the investigator must maintain records of all study medication delivery to the site, site inventory, use by each subject, and return to the sponsor or designee.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labeled storage conditions, and is in good condition. See pharmacy manual for receipt of shipments. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and notifying Takeda per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator must maintain 100% accountability for all study medication received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must record the current inventory of all study medication on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of study medication, expiry and/or retest date, date and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to who study medication is dispensed.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study

material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained before the subject enters into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (7 digit subject ID) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Pharmacogenomic Informed Consent Procedure

Pharmacogenomics informed consent is a component of the overall study informed consent. The requirements are described in Section 15.2.

9.1.3 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, alcohol and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the condition/disease under study that stopped at or before informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.9).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 1 year before signing of informed consent.

9.1.4 Safety Assessments

On Day 1, all the assessments must be reviewed by the investigator before randomization to assure eligibility requirements have been met. During the study, all assessments should be done before administration of study drug unless otherwise indicated.

9.1.4.1 Tuberculosis Screening

All subjects must have a screening test for tuberculosis. Either a tuberculin skin test or QuantiFERON $^{\mathbb{R}}$ is acceptable. If a tuberculin skin test is done, it should be interpreted according to the applicable local Health Authority or Medical Society guidelines providing recommendations for interpretation of tuberculin skin testing in subjects who are immunosuppressed or have a prior history of BCG vaccination or have a prior positive test.

Subjects with a positive screening test for tuberculosis will not be eligible for the study unless active tuberculosis infection is ruled out and treatment for latent tuberculosis has been completed at least 4 weeks before randomization.

9.1.5 Physical Examination Procedure

A baseline physical examination (defined as the pretreatment assessment immediately before the start of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

The physical examination should be done at Screening Visit, Baseline (defined as the pretreatment assessment immediately before the start of investigational drug), at the beginning of each cycle and, at the End of Treatment Period. Additional physical examinations can be done at any visit if necessary based on investigator's clinical judgment.

In particular the investigator should be alert for symptoms and signs of fluid disturbance from Gastro-Intestinal events, skin rashes and peripheral neuropathy. Ixazomib therapy may need to be interrupted, down titrated or stopped if these events occur (see Section 7.4.2)

Any abnormal change from the baseline physical examination (Day -1) must be assessed as not clinically significant (NCS) or clinically significant (CS) by the investigator and recorded in the source document and eCRF.

Any clinically significant change, as determined by the investigator, from the baseline physical examination will be recorded as an AE or pretreatment event in source documentation and on the Pretreatment Event/AE eCRF.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the pretreatment event/AE eCRF described in Section 10.0.

9.1.6 Weight, Height, and Body Mass Index

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The body mass index (BMI) is calculated using metric units with the formula provided below:

Metric:
$$BMI = weight (kg)/[height (m)]^2$$

Height will be collected in centimeters without decimal places and weight will be collected in kilograms to 1 decimal place. Results for BMI will be expressed with 1 decimal place.

Example:

-Height=176 cm (or 1.76 m), weight=79.2 kg; BMI=79.2/1.76 2 =25.6 kg/m 2 .

9.1.7 Vital Sign Procedure

During the Double-Blind Treatment Period, vital signs will be collected at Screening (Day -35 to -1) and on Cycle 1 and Cycle 2 at Days 1, 8, 15, and 22. In Cycle 3 vital signs will be collected on day 1, day 8, day 15, day 22 and Day 28 (Final Visit/End of Treatment (EOT)/ET) and at every follow-up visit. During the Open-Label Treatment Extension Period, vital signs will be collected before the first dose of each treatment cycle. Vital signs will include body temperature, sitting blood pressure (after 5 minutes resting), respiration rate, and pulse (beats per minute).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within approximately 0.5 hour before or after the scheduled blood draw.

9.1.8 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.9 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the Screening examination. The condition (ie, diagnosis) should be described.

9.1.10 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The approximate total volume of blood for the study is 453.5 mL if the subject <u>does not</u> participate in the Open-Label Treatment Extension Period or 493.5 mL if the subject <u>does</u> participate in the Open-Label Treatment Extension Period. Laboratory samples on Day 1 of each Cycle will be collected following a minimum 10-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Special
Red blood cells Reticulocytes White blood cells with differential Hemoglobin Hematocrit Platelets	Serum Chemistry Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase γ-Glutamyl transferase Total bilirubin Direct bilirubin Albumin Total protein Creatinine Blood urea nitrogen Creatine kinase Potassium Sodium Glucose Chloride Phosphorus Calcium	Urinalysis To be done at local laboratory pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis: RBC/high power field WBC/high power field Epithelial cells, casts, etc	To be done at local laboratory Coomb's test Platelets, red blood cells, white blood cells with differential To be done at central laboratory Lipid panel (fasted): Total cholesterol LDL-cholesterol HDL-cholesterol
		To be done at central laboratory Urine protein and creatinine for UPCR Urine Biomarkers To be done at the site Standard urinalysis using dipstick (protein only)	Triglycerides Serum complement C3 and C4 Total IgM, IgG and IgA Autoantibodies: Anti-double-stranded DNA Anti-nuclear antibody Anti-Ro (SS-A) Anti-La (SS-B) Anti-RNP Anti-Sm Anti-phospholipids Serum biomarkers Tetanus antibody titers HBsAb titers

Serum

Serum hCG (a)

At Screening Only:

Hepatitis panel, including HBsAg, and anti-HCV

FSH (b)

DNA=deoxyribonucleic acid, FSH=follicle-stimulating hormone, HBsAb=hepatitis B surface antibody, hCG=human chorionic gonadotropin, HDL=high-density lipoprotein, LDL=low-density lipoprotein.

- (a) Serum hCG pregnancy test will be done on all female subjects of childbearing potential at Screening.
- (b) The FSH level will be obtained for female subjects at Screening if they are postmenopausal by history (ie, last regular menstrual cycle >2 years) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use adequate contraception.

All Samples will be processed at the central laboratory with the exception of, urine microscopic analysis (RBC/high power field, WBC/high power field, epithelial cells, casts, etc) and Coomb's test, which should be processed at a local laboratory. Standard urinalysis (dipstick) should be done at study site. An additional sample for blood cell counting should be collected within

48 hours before each dosing and processed locally. Results from the blood cell counting done locally should be available before each dosing during the Double-Blind Treatment Period and before each cycle of the Open-Label Treatment Extension Period as specified in the Schedule of Events (Appendix A).

Urine samples for determination of UPCR should be processed by the central laboratory. Urine samples for UPCR analysis should be collected by the subject at home from the first void urine of the day on the 2 days before the visit and on the day of visit, totaling 3 samples as specified in Appendix A.

The central laboratory will also perform hematology and serum chemistry tests. The results of laboratory tests will be sent to the investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to Takeda or designee in the format requested by Takeda. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Detailed instructions for the handling and shipping of samples are provided in the laboratory manual.

Laboratory reports must be signed and dated by the principal investigator or sub investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All clinically significant laboratory abnormalities must be recorded as a pretreatment (PTE)/AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

Please refer to Section 7.4.1 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests. Follow-up laboratory tests for abnormal liver function test should include at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ -glutamyl transferase, and international normalized ratio.

Markedly Abnormal Laboratory Criteria for Hematology

The following markedly abnormal values will be used for hematology tests as part of the safety assessments defined in the primary endpoint of this study:

Parameter	Markedly Abnormal Value
Red blood cells	• <0.8× LLN if Baseline is ≥LLN, OR
Hemoglobin	 <0.8× pre-treatment value if Baseline is <lln< li=""> </lln<>
Neutrophils	• <0.65× LLN if Baseline is ≥LLN, OR
Lymphocytes Platelets	• <0.65× pre-treatment value if Baseline is <lln< td=""></lln<>

9.1.11 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 90 days after last dose of study medication, female subjects of childbearing potential must use 2 forms of adequate contraception. In addition they must be advised not to donate ova during this period.

Abstinence is not an acceptable method of contraception.

From signing of informed consent, throughout the duration of the study, and for 90 days after last dose of study medication, all male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (defined as continuous amenorrhea of at least 2 years and FSH>40 IU/L confirmed before any study medication is administered).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. Female subjects must use 2 effective methods of contraception, at the same time. In this study, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):

- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Intrauterine devices:

- Copper T PLUS condom and spermicide.
- Progesterone T PLUS condom and spermicide.

Hormonal contraceptives:

- Implants PLUS male condom and spermicide.
- Hormone shot/injection PLUS male condom and spermicide.
- Combined pill PLUS male condom and spermicide.
- Minipill PLUS male condom and spermicide.
- Patch PLUS male condom and spermicide.
- Vaginal ring PLUS male condom and spermicide.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they

understand the requirements for avoidance of pregnancy, donation of ova during the course of the study.

During the course of the study, regular serum or urine hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the Schedule of Study Procedures (Appendix A). In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine pregnancy test on Day 1 and throughout the study.

9.1.12 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. If the pregnancy occurs during administration of active study medication, eg, after Day 1 of Cycle 1 or within 90 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies in a subject receiving active study medication will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.13 ECG Procedure

A standard 12-lead ECG will be recorded at Screening, on Day 1 of each cycle and ET/EOT. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

When an ECG is scheduled at the same time as blood draws or vital signs then the blood draws and vital signs will take priority and the ECG will be obtained within 1.5 hours before or after the scheduled blood draw/vital sign assessment.

Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and OTcB (Fredericia's and Bazett's correction) intervals.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source.

All ECGs will be recorded at the time points detailed in the Schedule of Study Procedures (Appendix A).

9.1.14 Additional Assessments

9.1.14.1 *Urinalysis*

The urine sediment should be assessed at a local laboratory in a timely manner by an analyst trained in the assessment of cellular casts. Attention should be given to assure that hematuria or pyuria are clearly due to SLE and not due to menses, infection or contamination of the urine specimen. Investigators should make every effort to prevent urine sample contamination is avoided and exclude possible urinary tract infections. If abnormal white blood cell counts are observed in the urine specimen, the site should obtain additional urine samples for repeat analysis and urine culture to be done at the local laboratory.

For UPCR determination, urine samples will be collected at home and brought to the site by the subjects. The samples should be collected from the first void urine of the day on the 2 days before the visit and on the day of visit, totaling 3 samples and kept under refrigeration during storage. These urine samples will be sent to a central laboratory for analysis of protein and creatinine levels. All subjects enrolled in the study must be trained by a qualified member of the investigational site personnel to collect the urine sample in "clean catch" technique. UPCR will be calculated as mg/mg ratio.

9.1.14.2 eGFR

Renal function will be assessed through eGFR using the CKD-EPI formula below and expressed as mL/min/1.73 m²:

eGFR = 141 x min(SCr/k, 1) $^{\alpha}$ x max(SCr /k, 1) $^{-1.209}$ x 0.993 Age x (1.018 [if female]) x (1.159 [if black])

Where SCr is serum creatinine in mg/dL, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1 and max indicates the maximum of SCr/k or 1, and age in years.

9.1.14.3 Definition of Complete and Partial Renal Responses

For complete renal response, all of the following criteria must be met:

Renal Function	eGFR is normal OR no less than 85% of the lesser of the values at screening or randomization (Day 1)		
Proteinuria (UPCR)	UPCR <0.5		
Urine sediment	No cellular casts, based on assessment performed at local laboratory		

For partial renal response, all of the following criteria must be met:				
Complete response	Subject does not meet criteria for complete response			
Renal Function	eGFR is no less than 85% of the lesser of the values at screening or randomization (Day 1)			
Proteinuria (UPCR)	• ≥50% reduction in UPCR from Baseline and one of the following:			
	a) UPCR <1 if baseline value was ≤ 3 , OR			
	b) UPCR <3 if baseline value was >3.			
	Baseline is defined as the greater of the values at Screening or Randomization (Study Day 1)			
Urine sediment	No cellular casts, based on assessment performed at local laboratory			

No renal response is defined when subjects did not meet the criteria for either Complete Renal Response or Partial Renal Response.



9.1.14.5 Company Confidential Information

Company Confidential Information

9.1.15 Pharmacodynamic Sample Collection

Pharmacodynamic measures will include hematologic measures of serum anti dsDNA antibody, other autoantibodies and complement C3/C4 levels. Samples will be collected as noted in Appendix A. These assays are routinely performed in the central laboratory.

9.1.16 Pharmacogenomic and Other Sample Collection



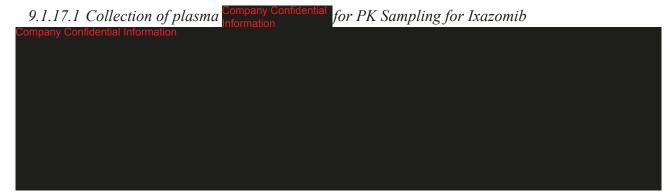
Also because PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored DNA and RNA samples.

The PGx samples will be stored for no longer than 15 years after completion of the ixazomib study and/or until the drug development of ixazomib is no longer actively pursued by Takeda or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with a 7 digit subject ID (with 4 digit the site + 3 digit subject number) issued by TDC. The dataset with masked identity are intended for the association analysis of ixazomib.

Protein and other biomarker profiling, serum and urine (10 mL samples) will be collected at multiple endpoints as indicated in Appendix A. Samples will be stored at -20°C until shipped. Frozen samples will be shipped on dry ice to laboratories with appropriate expertise in analysis of these markers. Both the urine and serum will be analyzed for markers relevant to inflammation

Detailed instructions for the handling and shipping of samples are provided in the laboratory manual

9.1.17 PK Sample Collection



Serial blood samples for determination of ixazomib concentrations will be collected according to Table 9.b for the Double-Blind Treatment Period. Detailed instructions for the handling and shipping of samples are provided in the laboratory manual.

Table 9.b Collection of Blood Samples for PK Analysis during the Double-Blind **Treatment Period**

Sample Type		Time Postdose
Plasma	Cycle 1	Predose (within 0.5 hour before dosing) on Days 1, 8, and 15. On Day 1 of Cycle 1, sample will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, and 168 (predose Day 8) hours following the first dose.
	Cycle 2	Predose (within 0.5 hour before dosing) on Days 1, 8, and 15. Samples will be collected on Day 22 (168 hours postdose on Day 15) in Cycle 2.
	Cycle 3	Predose (within 0.5 hour before dosing) on Days 1, 8, and 15. On Day 15 following the third dose, samples will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 168, and 312 hours postdose in Cycle 3.

The actual time of sample collection will be recorded on the source document and eCRF.

There will be no PK sampling during the Open-Label Treatment Extension Period.

9.1.17.2 Bioanalytical Methods

Plasma concentrations of ixazomib will be measured by high-performance liquid chromatography with tandem mass spectrometry within a validated range of 0.500 to 500 ng/mL.

Company Confidential Information

9.1.18 PK Parameters

The PK parameters of ixazomib will be determined from the concentration-time profiles for all evaluable subjects using non-compartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving sampling times. The following PK parameters may be calculated, as permitted by the data, from plasma concentrations of ixazomib:

Symbol/Term	Definition					
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity.					
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.					
AUC_t	Area under the plasma concentration-time curve from the time 0 to time t.					
Company Confidential	Information					
AUC_{168}	Area under the plasma concentration-time curve from 0 to 168 hours					
Company Confidential I	nformation					
CL/F	Apparent clearance after oral administration, calculated as $CL/F=Dose/AUC_{\infty}$					
C_{max}	Maximum observed plasma concentration.					
Company Confidential I	nformation					
Company Confidential Ir	iformation					
Company Confidential	Information					
t _{max}	time of first occurrence of C _{max}					

Additional PK parameters may be calculated as appropriate.

A population PK model-based analysis may be performed in addition to the noncompartmental analysis to describe the PK of ixazomib in LN patients. If performed, the details of the analysis will be provided in a separate analysis plan and report.

9.1.19 Preparation, Reconstitution, and Dispensation

The investigational pharmacist or designee will prepare the study treatment under standard aseptic conditions. More details on the preparation of study treatment are provided in the Pharmacy Manual.

9.1.20 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- Pretreatment event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Major protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal, specify reason.
- Study termination.
- Other, specify reason.

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.21 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered on Days 1, 8, and 15 of each cycle while subjects are under observation in the clinical research site. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

During the Open-Label Treatment Extension, the first dose of each cycle will occur while subjects are in the clinic, and the remaining doses will be self-administered at home.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Subjects will be screened for the study within 24 (+11) days before the first dose of study medication. Subjects will be screened in accordance with predefined inclusion and exclusion

criteria as described in Section 7.0. See Section 9.1.19 for procedures for documenting screening failures. If the elapsed time between Screening Visit and Randomization (Day 1) is greater than allowed screening period, then the eligibility criteria must be re-confirmed in a second screening visit before randomization.

9.3.1.1 Screening Visit

Procedures to be completed at Screening Visit include:

- Informed consent.
- Inclusion/exclusion criteria review.
- Demographics, medical history, and medication history.
- Physical examination.
- Renal biopsy history.
- Stabilize concomitant medications (if needed).
- Vital signs.
- Weight, height, and BMI.
- Concomitant medications.
- Concurrent medical conditions.
- ECG procedure.
- Pregnancy test [Serum hCG test (females of childbearing potential only)].
- Pretreatment event assessment.
- TB screening.
- FSH (only postmenopausal women by history and not surgically sterile).
- HBsAg and Anti-HCV.
- Hematology panel.
- Chemistry panel.
- Urinalysis (including microscopic analysis).
- Urine sample for protein/creatinine ratio.
- Urine dipstick protein.
- Serum complement (C3, C4).
- Anti-dsDNA.
- Coomb's test direct.

- Quantitative IgG.
- Company Confidential
- Pregnancy avoidance counseling.
- Access IVRS/IWRS to obtain subject number.
- Dispense urine cups for UPCR collection before Day 1 Visit (on Day -2, Day-1 and Day 1).

Procedures to be completed at the **second Screening Visit include (if visit is needed):**

- Hematology panel.
- Chemistry panel.
- Urinalysis (including microscopic analysis).
- Urine sample for protein/creatinine ratio.
- Urine dipstick protein.
- Serum complement (C3, C4).
- Coomb's test direct.
- Anti-dsDNA.
- Urine pregnancy test.
- Company Confidential

9.3.2 Randomization

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized as described in Section 8.2. Subjects will be administered the first dose of study medication in the unit under the supervision of the investigator or designee, as described in Section 8.2. The procedure for documenting Screening failures is provided in Section 9.1.19.

9.3.2.1 Day 1 (Cycle 1, 2 and 3)

- Inclusion/exclusion criteria review [Day 1 of Cycle 1].
- Physical examination.
- Neuropathy assessment (functional assessment of cancer therapy [FACT]/GOG-NTX).
- Vital signs assessment.
- Weight.
- Medical history [Day 1 of Cycle 1 only].
- Review of concomitant medications.

- Concurrent medical conditions [Day 1 of Cycle 1 only].
- Hematology panel.
- Chemistry panel.
- Lipid panel.
- Urinalysis (including microscopic analysis).
- Urine sample for protein/creatinine ratio.
- Serum complement (C3, C4).
- Anti-dsDNA.
- Coomb's test direct.
- Quantitative IgG, IgM, and IgA [Day 1 of Cycle 1 only].
- Serum collection for biomarkers [Day 1 of Cycle 1 only].
- Urine collection for biomarkers [Day 1 of Cycle 1 only].
- RNA collection [Day 1 of Cycle 1 only].
- DNA collection [Day 1 of Cycle 1 only].
- PK blood collection.
- ECG.
- Company Confidential
- Company Confidential
- Urine dipstick protein.
- Urine pregnancy test.
- Tetanus antibody titers.
- Hepatitis B surface antibody titer.
- Platelets, red blood cells, white blood cells with differential (within 48 hours before dosing).
- Access IVRS/IWRS.
- Pregnancy avoidance counseling.
- Study medication dosing in the clinic.
- Overnight fast.
- AE assessment.

9.3.2.2 Day 2 (Cycle 1)

- PK blood collection.
- RNA collection.
- AE assessment.
- Serum collection for biomarkers.
- Urine collection for biomarkers.

9.3.2.3 Day 8 (Cycle 1, 2 and 3)

- Vital signs assessment.
- Review of concomitant medications.
- Hematology panel.
- Chemistry panel.
- PK blood collection.
- Urine pregnancy test.
- Access IVRS/IWRS.
- Pregnancy avoidance counseling.
- Study medication dosing in the clinic.
- AE assessment.
- Serum collection for biomarkers [Day 8 of Cycle 1 only].
- Urine collection for biomarkers [Day 8 of Cycle 1 only].
- Platelets, red blood cells, white blood cells with differential (within 48 hours before dosing).
- Dispense urine cups for UPCR collection before Day 15 Visit.

9.3.2.4 Day 15 (Cycle 1, 2 and 3)

- Vital signs assessment.
- Review of concomitant medications.
- Hematology panel.
- Chemistry panel.
- Urine sample for protein/creatinine ratio.
- Serum complement (C3, C4).

- Anti-dsDNA.
- PK blood collection.
- Urinalysis (including microscopic analysis).
- Urine pregnancy test.
- Platelets, red blood cells, white blood cells with differential (within 48 hours before dosing).
- Access IVRS/IWRS.
- Pregnancy avoidance counseling.
- Study medication dosing in the clinic.
- AE assessment.

9.3.2.5 Day 16 (Cycle 3 only)

- PK blood collection.
- AE assessment.

9.3.2.6 Day 22 (Cycle 1, 2 and 3)

- Vital signs assessment.
- Review of concomitant medications.
- Hematology panel.
- Chemistry panel.
- Quantitative IgG, IgM, and IgA [Day 22 of Cycle 1 and 2].
- PK blood collection [Day 22 of Cycle 2 and Cycle 3].
- Pregnancy avoidance counseling.
- AE event assessment.
- Dispense urine cups for UPCR collection before Day 1 [Day 1 of Cycle 2 and Cycle 3] and before Day 28 of Cycle 3.

9.3.3 End of Treatment Visit/Early Termination/Final Visit

End of Treatment / Final Visit will be scheduled on Day 84 (±2 days) of the Double-Blind Treatment Period and Day 168 (±2 days) of the Open Label Treatment Extension Period. For an Early Termination Visit the reason for an early discontinuation must be documented in the source document and eCRF.

9.3.3.1 Day 28 (Cycle 3)/Final Visit/ET/EOT

- Physical examination.
- Neuropathy assessment (FACT/GOG/NTX).
- Weight.
- Vital signs assessment.
- Review of concomitant medications.
- Hematology panel.
- Chemistry panel.
- Lipid panel.
- Serum complement (C3, C4).
- Anti-dsDNA.
- Company Confidential Information
- Coomb's test-direct.
- Quantitative IgG, IgM, and IgA.
- PK blood collection (not applicable in the Open Label-Treatment Extension Period).
- Urinalysis (including microscopic analysis).
- Urine sample for protein/creatinine ratio.
- Urine dipstick protein.
- RNA collection (not applicable in the Open Label-Treatment Extension Period).
- ECG.
- Company Confidential
- Company Confidential
- Urine pregnancy test.
- Tetanus antibody titers.
- Hepatitis B surface antigen antibody titer.
- Access IVRS/IWRS.
- Pregnancy avoidance counseling.
- AE assessment.
- Overnight fasting.

9.3.4 Open-Label Treatment Extension

- Physical examination (Day 1 of each Cycle).
- Concurrent medical conditions [Day 1 of Cycle 1 only].
- Weight (Day 1 of each Cycle).
- Vital signs assessment (Day 1 of each Cycle).
- AE assessment.
- Review of concomitant medications (Day 1 of each Cycle).
- Pregnancy avoidance counseling (Day 1 of each Cycle).
- Urine pregnancy test.
- Study drug dosing (Days 1, 8, 15 of each Cycle).
- ECG (day 1 of each Cycle).
- Hepatitis B surface antibody titer (Day 1 of Cycles 1 and 3).
- Tetanus antibody titers (Day 1 of Cycles 1 and 3).
- Hematology panel (Day 1 of each Cycle).
- Platelets, red blood cells, white blood cells with differential (within 48 hours before dosing as specified in Appendix A.
- Chemistry panel (Day 1 of each Cycle).
- Urinalysis (including microscopic analysis) (Day 1 of each Cycle).
- Urine sample for protein/creatinine ratio (Day 1 of each Cycle).
- Serum complement (C3, C4) (Day 1 of each Cycle).
- Anti-dsDNA (Day 1 of Cycle 1 only).
- Company Confidential Information
- Coomb's test direct (Day 1 of each Cycle).
- Quantitative IgG, IgM, and IgA (Day 1 of each Cycle).
- Neuropathy assessment (FACT/GOG/NTX).
- Company Confidential Information
- Company Confidential Information
- Access IVRS/IWRS (Day 1 of each Cycle).

9.3.5 Follow-up Visit

The Follow-up Visit for the Double-Blind Treatment Period will occur monthly from Days 85 to 168 (± 7 days). The Follow-up Visit for the Open Label Treatment Extension Period will occur 30 days after the last open label treatment cycle (Cycle 3 Day 28; ± 7 days). All subjects who enter the open label treatment period will have monthly visits up to at least Day 168. If open label treatment is terminated before the completion of all 3 cycles, an end of treatment visit will be performed (Day 28 of current cycle) and the subsequent cycle day 1 visits will be replaced with a follow-up visit. Follow procedures listed in Appendix A.

- Physical examination [last follow-up only].
- Weight [last follow-up only].
- Vital signs assessment.
- Chemistry panel.
- Hematology panel.
- Lipid panel [last follow-up only].
- Serum complement (C3, C4).
- Anti-dsDNA.
- Company Confidential Information
- Coomb's test-direct.
- Quantitative IgG, IgM, and IgA [last follow-up only].
- Company Confidential
- Company Confidential
- Urinalysis (including microscopic analysis).
- Urine sample for protein/creatinine ratio
- Urine dipstick protein.
- Urine pregnancy test.
- Tetanus antibody titers [last follow-up only].
- Hepatitis B surface antigen antibody titer [last follow-up only].
- AE assessment.
- Dispense urine cups for UPCR collection.
- Pregnancy avoidance counseling.
- Overnight fasting [last follow-up only].

• Neuropathy assessment (FACT/GOG/NTX) (last follow-up of Open Label Treatment Extension Period only).

9.4 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c.

Table 9.c Approximate Blood Volume

	Blood Volume Collected (mL)							
				Double-Bli	nd Trea	ntment)		
Day	-24(-11) to -1	1	2	8		15	22	Total (mL)
Sample Type								
Safety laboratory	22	23 (b) (f)		13(b)	$(f) \mid 2$	3 (b) (f)	10	91
samples								
Plasma PK samples Company Confidential I		24 (a)	3	3 (a,t)	3 (b)		33
Company Confidential II	ntormation							
Serum biomarkers		3 (b)	3	3				9
DNA sample		10						10
RNA samples		12.5	2.5					15
	Total Blood	l Volume for	Screenin	g and in Cy	ycle 1			170
		Cycle 2 (Double-Blind Treatment)						
Day		1	8]	15	22	Total (mL)
Sample T	ype							
Safety laboratory samples (b)		20	13 (f)		23 (f)		10	66
Plasma PK s Company Confidential I	amples	3 (b)	3 (b)		3	3 (b)		12
Company Confidential I	Information							
	To	otal Blood V	olume in (Cycle 2				80
			Cycle 3	(Double-Bl	ind Tre	atment)		
Day		1	8	15	16	22	28	Total (mL)
Sample T	Гуре							
Safety laboratory samples (b)		24	13 (f)	23 (f)		10	20	90
Plasma PK samples		3 (b)	3 (b)	24 (c)	3	3	3	39
Company Confidentia	l Information							· · · · · · · · · · · · · · · · · · ·
RNA sam	ples						2.5	2.5
		Total	Blood Volu	me in C	Cycle 3		143.5	

Footnotes are on last table page.

 Table 9.c
 Approximate Blood Volume (continued)

	Follow-up Period (d) (No Open Label Treatment)					Total (mL)
Month	Month 4		Month 5		Month 6	
Sample Type						
Safety laboratory samples	20		20		20	60
Total E	Blood Volume	in the Follo	w-up Perio	<u></u>		60
	Open Label Treatment Period and Follow-up (g)					Total (mL)
	Cycle 1	Cycle 2	Cycle 3	ET/EOT/Fin	Follow-up	
				al Visit	visit	
Safety laboratory samples	20 (b) (f)	20(b) (f)	20 (b) (f)	20	20	100
Total E	Blood Volume	in the Follo	w-up Perio	d		100
Total Approximate Blood Volun	` /	over the stu	•	collected per	Subject (no	453.5
R	•		,			
otal Approximate Blood Volum	e (mL) to be	over the stu	dv duration	collected per S	Subject (with	493.5

Direct venipuncture is the only acceptable method of blood collection.

- (e) Company Confidential Information
- (f) Collection should occur within 48 hours before visits on the day of dosing of each cycle with results required back to the site before dosing.
- (g) Open Label Treatment Period and Follow-up consists of up to 3 additional cycles of treatment (Day 85 to 168) with a Follow-up visit 30 days after the last dosing.

⁽a) Plasma PK samples collected in Cycle 1 on Day 1: Predose (within 0.5 hour before dosing) on Days 1, 8, and 15. On Day 1 of Cycle 1, following the first dose, sample will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, and 168 (predose Day 8) hours postdose. (b) Predose.

⁽c) Plasma PK samples collected in Cycle 3 Predose (within 0.5 hour before dosing) on study Days 1, 8, and 15. On Day 15 of Cycle 3 following the third dose, samples will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 168 and 312 hours postdose in Cycle 3. (d) Follow-up visits on Days 112, 140, and 168.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

• Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

• Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory retest and/or continued monitoring of an abnormal value are not considered an

- intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of...").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of...").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of...").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of...").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of...").

Changes in severity of AEs /Serious PTEs:

• If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

Preplanned procedures (surgeries or therapies) that were scheduled before signing of
informed consent are not considered PTEs or AEs. However, if a preplanned procedure is
performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the
worsening of the condition should be captured appropriately as a PTE or an AE.
Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

• Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

• Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

- 1. Results in DEATH.
- 2. Is LIFE THREATENING.
 - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- 3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
- 4. Results in persistent or significant DISABILITY/INCAPACITY.
- 5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
- 6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.
 - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

	Term		
Acute respiratory failure/acute respiratory distress	Hepatic necrosis		
syndrome	Acute liver failure		
Torsade de pointes / ventricular fibrillation / ventricular	Anaphylactic shock		
tachycardia	Acute renal failure		
Malignant hypertension	Pulmonary hypertension		
Convulsive seizures	Pulmonary fibrosis		
Agranulocytosis	Confirmed or suspected endotoxin shock		
Aplastic anemia	Confirmed or suspected transmission of infectious agent by		
Toxic epidermal necrolysis/Stevens-Johnson syndrome	a medicinal product		
	Neuroleptic malignant syndrome / malignant hyperthermia		
	Spontaneous abortion / stillbirth and fetal death		

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Management of Clinical AEs of Interest

10.1.5.1 Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, the administration of antidiarrheals once infectious causes are excluded may be considered. Fluid intake should be strictly maintained to avoid dehydration.

10.1.5.2 Nausea and/or Vomiting

Although this study will not initially employ prophylactic anti-emetics, there is no prohibition against their use in the management of a patient who develops nausea and/or vomiting after receiving ixazomib. The use of anti-emetics such as serotonin receptor antagonists may be considered if clinically required.

10.1.5.3 Volume Depletion

Dehydration should be avoided. Two cases of acute renal failure have been reported in patients treated at or above the MTD for IV ixazomib. NSAIDs should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function. Additionally, volume depletion should be corrected before initiation of study drug.

10.1.5.4 Renal AEs

Urinary excretion of the parent compound is negligible, but modest transient increase in creatinine and infrequent (<10%) cases of reversible renal failure have been reported in oncology subjects receiving ixazomib, albeit with confounding factors such as GI fluid loss or high does

NSAIDs, factors which are addressed above. Subjects in this study will have weekly monitoring of laboratory parameters including creatinine and ixazomib will be discontinued if a >25% decrease in eGFR or a doubling in serum creatinine are observed.

10.1.5.5 Erythematous Rash With or Without Pruritus

Rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested. The rash has been transient and has resolved either spontaneously or with standard symptomatic measures such as oral or topical antihistamines. The rash may range from some erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. Prophylactic measures should also be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone <10 mg per day or equivalent is permitted.

Severe, life-threatening or fatal conditions that may involve rash, blistering, skin peeling and mouth sores including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and pemphigus vulgaris are a rare risk which have been reported in ixazomib oncology studies when given in combination with other drugs. Due to limited experience and because these conditions occurred while patients were receiving other drugs as well, it is not known whether they were caused by ixazomib. The subject should be discontinued from study drug if they are diagnosed with any of these conditions and should be managed symptomatically according to standard medical practice. In addition, all subjects with rash grade 3 or greater must have punch biopsies and dermatology consult. It is recommended taking pictures of the rash.

10.1.5.6 Thrombocytopenia

Thrombocytopenia has been reported to date primarily at the higher doses tested. Blood counts should be monitored regularly as outlined in Section 7.4.3 with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Administration of ixazomib should be modified as noted as per dose modification recommendations as described in Section 7.4.3 when thrombocytopenia occurs. Therapy with ixazomib can be reinitiated at a reduced level upon recovery of platelet counts.

10.1.5.7 Prophylaxis Against Risk of Infection

If lymphopenia is noted, patients may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir or valacyclovir may be initiated at the onset of administration of ixazomib. Other antivirals are also acceptable.

10.1.5.8 Peripheral Neuropathy

With preliminary clinical data collected thus far, mild and reversible peripheral neuropathy has been reported. Therefore, patients on ixazomib should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain, or weakness. In cases of new or worsening sensory peripheral neuropathy, with or without pain, dose adjustment or stopping of ixazomib may be required.

10.1.5.9 Hypoglobulinemia

In case that total immunoglobulin levels drops to less than 50% of the lower limits of normal, ixazomib should be discontinued and IV Immunoglobulins (IVIg) therapy is recommended to increase total immunoglobulin levels.

10.1.6 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities. Severe: The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Yes: An AE that follows a reasonable temporal sequence from administration of a drug (including

the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications,

concomitant drugs and concurrent treatments, may also be responsible.

No: An AE that does not follow a reasonable temporal sequence from administration of a drug

and/or that can reasonably be explained by other factors, such as underlying diseases,

complications, concomitant drugs and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Yes if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as No.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Day 1) or until screen failure. For subjects who discontinue before study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until the Final Visit (168 ± 7 days) after the first dose of study drug).

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and stop date and time.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of study medication(s) (yes or no) (not completed for PTEs).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study medication (not applicable for PTEs).
- Outcome of event.
- Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed in the eCRF, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be completed in the eCRF within 24 hours of first onset or notification of the event. In the event that the EDC system is unavailable for SAE reporting, the back-up SAE paper form should be completed and transmitted to Takeda Pharmacovigilance or designee within 24 hours of first onset or notification of the event to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, a liver function test increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.1.10 must also be performed. In addition, a liver function test increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes

(eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, suspected unexpected serious adverse reactions will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

Eligibility for the study is intended to be confirmed by an adjudication committee consisting of Takeda and external experts not directly involved in the study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 Electronic CRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are entered directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the database lock of clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign, and date the form.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms,

subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before unblinding of subject's treatment and before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

Safety Set:

The Safety Analysis Set will consist of all subjects who are enrolled and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

PK Set:

The PK set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration.

Pharmacodynamic Set:

The PD set will consist of all subjects who receive study drug and have at least 1 postdose PD measurement.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, and BMI) for pooled placebo, each ixazomib dose level, and ixazomib overall. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (gender, ethnicity, and race) will be tabulated for pooled placebo group, each ixazomib dose level, and ixazomib overall. Individual subject demographic and baseline characteristics data will be listed. Placebo data will be pooled across the cohorts.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for subjects who are screened, but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

13.1.3 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical condition verbatim reported terms will be coded to the closest matching lower level term and then to the first listed preferred term (PT) and system

organ class (SOC) using MedDRA. All medical history and concurrent medical conditions will be listed.

13.1.4 Medication History and Concomitant Medication

Medications taken within 28 days before the Screening Visit and stopped before the Screening Visit will be recorded in the medication history eCRF. Medications taken during or after the Screening Visit will be considered as concomitant medications. Medications started before the Screening Visit and continued will also be considered as concomitant medications. Medication history and concomitant medications will be coded using WHO Drug. All medication history and concomitant medications data will be listed.

13.1.5 PK Analysis

Concentrations of ixazomib in plasma and confidential will be summarized by ixazomib dose level at each scheduled sampling time using descriptive statistics (N, arithmetic mean, SD, median minimum, maximum and percent coefficient of variation (%CV)). Individual plasma concentration data versus time will be presented in a data listing.

PK parameters of ixazomib will be summarized for each dose level using descriptive statistics. In addition, geometric mean will be computed for C_{max} and AUCs. Dose proportionality will be assessed graphically and using the power model.

Plots of C_{max} and AUCs, as well as dose-normalized Cmax and AUCs, versus doses will be generated.

Other analyses or methods may be used, if appropriate.

13.1.6 Pharmacodynamic and Exploratory Analysis

Individual values and changes in the levels of anti-dsDNA antibodies, complement C3/C4 levels, and UPCR will be summarized.

Individual changes from baseline in serum and urine biomarkers will be summarized.

13.1.7 Safety Analysis

For all safety summary tables stated under this section, the tables will be summarized by placebo, each ixazomib dose level and ixazomib overall. Placebo data will be pooled across the dose levels.

13.1.7.1 AEs

All PTEs and TEAEs will be coded by SOC and PT using MedDRA. TEAEs with onset occurring within 30 days (onset date – last date of dose $+1 \le 30$) after the last study drug administration will be listed, and included in the summary tables.

The TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug

(related vs. not-related), severity of AEs and related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs.

13.1.7.2 Kidney function Evaluation

Baseline, postdose, and change from Baseline to postdose data will be summarized. All SCr and eGFR data will be listed.

13.1.7.3 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet TDC's markedly abnormal criteria to be defined in the SAP will be listed and summarized in groups. Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized. All clinical laboratory data will be listed.

13.1.7.4 Vital Signs

Individual results of vital signs that meet TDC's markedly abnormal criteria to be defined in the SAP will be listed and summarized. Baseline, postdose, and change from Baseline in vital sign measurements will be summarized. All vital signs data will be provided in the data listings.

13.1.7.5 Electrocardiograms

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet TDC's markedly abnormal criteria to be defined in the SAP will be listed and summarized. Baseline, postdose, and change from Baseline in quantitative ECG parameters will be summarized. Shift tables will be generated for the investigator's ECG interpretations. All ECG data will be provided in the data listings.

13.2 Interim Analysis and Criteria for Early Termination

There will be no unblinded interim analysis. A blinded safety analysis may be conducted after 5 subjects are enrolled in the 4 mg cohort. An independent physician/designee will periodically monitor the overall conduct of the study to safeguard the interests of study participants including to make recommendations relating to the eligibility of subjects entering the Open-Label Treatment Extension Period, as well as monitoring their progress while receiving extended treatment.

13.3 Determination of Sample Size

This study is not statistically powered for any hypothesis testing. The sample size of at least 4 active and 1 placebo subjects for each of the 0.5 mg and 2.0 mg dose groups (Cohorts A and B, respectively), 6 active and 2 placebo subjects for each of the 3.0 and 4.0 mg dose groups (Cohorts C and D, respectively) is considered to be sufficient to fulfill the study objectives of the evaluation of safety, tolerability, and PK of each cohort.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the medical monitor (and IRB or IEC, as required) to determine the appropriate course of action.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. However, blood samples not collected within the interval specified for the scheduled sample time should be reported to Takeda and recorded in the source documents.

The Significant Protocol Deviation eCRF is to be completed for deviations that are identified by the sponsor before study start.

Table 14.a Windows for PK Sample Collection (Cycle 1 and Cycle 3)

Time Window	Nominal Sampling Time
no more than 0.5 h predose	0 hour
±0.5 min	15 and 30 min
±0.25 h	1 h, 1.5 h, 2
$\pm 0.75 \text{ h}$	4 h
± 1.0 h	8 h
± 2.0 h	24 h
± 8 h	>72 h to ≤316 h

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will [ship drug/notify site] once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received written permission from competent authority to begin the trial. Until the site receives [drug/notification] no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a pharmacogenomic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in

accordance with this section and the Master Services Agreement or equivalent agreement. In the event of any discrepancy between the protocol and the Master Services Agreement or equivalent agreement the Master Services Agreement or equivalent agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Takeda will, at a minimum, register all clinical trials conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation.

15.4.3 Clinical Trial Results Disclosure

Takeda will minimally post the results of clinical trials conducted in patients, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Master Services Agreement or equivalent agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

- 1. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med 2008;358(9):929-39.
- 2. Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. Arthritis Res Ther 2012;14 Suppl 4:S4.
- 3. Grossman JM. Lupus arthritis. Best Pract Res Clin Rheumatol 2009;23(4):495-506.
- 4. Sacks JJ, Luo Y-H, Helmick CG. Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the United States, 2001-2005. Arthritis care & research 2010;62(4):460-4.
- 5. Pons-Estel GJ, Alarcon GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum 2010;39(4):257-68.
- 6. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15(2):241-50.
- 7. Borchers AT, Leibushor N, Naguwa SM, Cheema GS, Shoenfeld Y, Gershwin ME. Lupus nephritis: a critical review. Autoimmun Rev 2012;12(2):174-94.
- 8. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64(6):797-808.
- 9. Dall'Era M, Stone D, Levesque V, Cisternas M, Wofsy D. Identification of biomarkers that predict response to treatment of lupus nephritis with mycophenolate mofetil or pulse cyclophosphamide. Arthritis Care Res (Hoboken) 2011;63(3):351-7.
- 10. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum 2004;50(12):3934-40.
- 11. Smith RM, Clatworthy MR, Jayne DR. Biological therapy for lupus nephritis-tribulations and trials. Nat Rev Rheumatol 2010;6(9):547-52.
- 12. Houssiau FA, Isenberg D. Towards treating lupus nephritis without oral steroids: a dream-come-true? Ann Rheum Dis 2013;72(8):1271-2.
- 13. Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney inter, Supple 2012;2:139-274.
- 14. Manz RA, Radbruch A. Plasma cells for a lifetime? Eur J Immunol 2002;32(4):923-7.
- 15. van Tol MJ, Gerritsen EJ, de Lange GG, van Leeuwen AM, Jol-van der Zijde CM, Oudeman-Gruber NJ, et al. The origin of IgG production and homogeneous IgG components after allogeneic bone marrow transplantation. Blood 1996;87(2):818-26.

- 16. Mohty M, Brissot E, Savani BN, Gaugler B. Effects of bortezomib on the immune system: a focus on immune regulation. Biol Blood Marrow Transplant 2013;19(10):1416-20.
- 17. Perry DK, Burns JM, Pollinger HS, Amiot BP, Gloor JM, Gores GJ, et al. Proteasome inhibition causes apoptosis of normal human plasma cells preventing alloantibody production. Am J Transplant 2009;9(1):201-9.
- 18. Hirai M, Kadowaki N, Kitawaki T, Fujita H, Takaori-Kondo A, Fukui R, et al. Bortezomib suppresses function and survival of plasmacytoid dendritic cells by targeting intracellular trafficking of Toll-like receptors and endoplasmic reticulum homeostasis. Blood 2011;117(2):500-9.
- 19. Neubert K, Meister S, Moser K, Weisel F, Maseda D, Amann K, et al. The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. Nat Med 2008;14(7):748-55.
- 20. Hainz N, Thomas S, Neubert K, Meister S, Benz K, Rauh M, et al. The proteasome inhibitor bortezomib prevents lupus nephritis in the NZB/W F1 mouse model by preservation of glomerular and tubulointerstitial architecture. Nephron Exp Nephrol 2012;120(2):e47-58.
- 21. Gupta N, Diderichsen PM, Hanley MJ, Berg D, van de Velde H, Harvey RD, et al. Population Pharmacokinetic Analysis of Ixazomib, an Oral Proteasome Inhibitor, Including Data from the Phase III TOURMALINE-MM1 Study to Inform Labelling. Clinical Pharmacokinetics 2017:1-14.
- 22. Gupta N, Zhao Y, Hui AM, Esseltine DL, Venkatakrishnan K. Switching from body surface area-based to fixed dosing for the investigational proteasome inhibitor ixazomib: a population pharmacokinetic analysis. Br J Clin Pharmacol 2015;79(5):789-800.
- 23. NINLARO® (Ixazomib) [Package Insert]. 25 Efal St., Petach Tikva 4951125: Takeda Israel Ltd., August, 2016.
- 24. van der Vlag J, Berden JH. Proteasome inhibition: a new therapeutic option in lupus nephritis? Nephrol Dial Transplant 2008;23(12):3771-2.

Appendix A Schedule of Study Procedures: Double-Blind Treatment Period

		Cyc Vis	eles 1 (28-Day	y Cycl 2 day	e) s	Cyc Vi:	eles 2 (28 sit Wind	3-Day C	ycle) ays		C	Sycles 3 (Visit Wi	(28-Day ndow ±2	Cycle) 2 days		Follow Up Visits every 4 weeks from Day 85 to Study completion Day 168 (±7 days)
	Screening (a)															ET /EOT/ Final Visit	
Days	-24 (-11) to -1	1	2	8	15	22	1	8	15	22	1	8	15	16	22	28	
Study Procedure																	
Informed consent (b)	X																
Inclusion/ exclusion criteria	X	X															
Demographics	X																
Medical history	X	X (c)															
Medication history	X																
Renal biopsy history	X																
Physical examination (c)	X	X (c)					X				X					X	X(m)
Concurrent medical conditions	X	X															
Stabilize concomitant medications (if needed)	X																
Weight	X	X					X				X					X	X(m)
BMI	X																
Height	X																
Vital signs (d)	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X

Appendix A Schedule of Study Procedures: Double-Blind Treatment Period (continued)

			vcles 1 (isit Wi					eles 2 (28 sit Wind				(Cycles 3 Visit W	(28-Day indow ±	/ Cycle) 2 days		Follow Up Visits every 4 weeks from Day 85 to Study completion Day 168 (±7 days)
	Screening (a)															ET /EOT/ Final Visit	
Days	-24 (-11) to -1	1	2	8	15	22	1	8	15	22	1	8	15	16	22	28	
Study Procedure																	
PTE assessment	X																
AE Assessments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitoring of concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X		X	X	
Pregnancy avoidance counseling	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X
Overnight fast		X					X				X					X	X(m)
Study drug dosing		X		X	X		X	X	X		X	X	X				
12-lead ECG (e)	X	X					X				X					X	
TB screening	X																
HBsAb and TT antibody titers		X									X					X	X(m)
FSH (l)	X																
HBsAg and Anti-HCV	X																
Hematology (f)	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X
Chemistry panel (f)	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X

Appendix A Schedule of Study Procedures: Double-Blind Treatment Period (continued)

					Day Cycl v ±2 day				3-Day Cy low ±2 d			(Cycles 3 (Visit Wi	(28-Day	Cycle) 2 days		Follow Up Visits every 4 weeks from Day 85 to Study completion Day 168 (±7 days)
	Screening (a)															ET /EOT/ Final Visit	
Days	-24 (-11) to -1	1	2	8	15	22	1	8	15	22	1	8	15	16	22	28	
Study Procedure																	
Lipid panel (fasted):		X					X				X					X	X(m)
Platelets counts white blood cells with differentiation and red blood cells (p)		X		X	X		X	X	X		X	X	X				
Pregnancy test (g)	X	X		X	X		X	X	X		X	X	X			X	X
Urinalysis (including microscopic analysis)	X	X			X		X		X		X		X			X	X
Urine sample for protein/creatinine ratio	X(o)	X(o)			X(o)		X(o)		X(o)		X(o)		X(o)			X	X(o)
Serum complement (C3, C4)	X	X			X		X		X		X		X			X	X
Anti-dsDNA	X	X			X		X		X		X		X			X	X
Company Confidential I	nformation																
Coomb's test-direct	X	X					X				X					X	X
Quantitative IgM and IgA		X				X				X						X	X(m)

Appendix A Schedule of Study Procedures: Double-Blind Treatment Period (continued)

		C	ycles 1 Visit W	(28-Daindow	ay Cyo ±2 da	ele) ys	Cyc Vis	les 2 (28 it Wind	-Day Cy ow ±2 d	vcle) ays		(Cycles 3 Visit Wi	(28-Day indow ±	Cycle) 2 days		Follow Up Visits every 4 weeks from Day 85 to Study completion Day 168 (±7 days) (q)
	Screening (a)															ET /EOT/ Final Visit	
Days	-24 (-11) to -1	1	2	8	15	22	1	8	15	22	1	8	15	16	22	28	
Study Procedure																	
Quantitative IgG	X	X				X				X						X	X(m)
DNA collection (h)		X															
RNA collection(i)		X	X													X	
Urine dipstick protein	X	X					X				X					X	X
Urine collection for biomarker		X	X	X													
Serum collection for biomarker		X	X	X													
PK Blood Collection plasma (j)		X	X	X	X		X	X	X	X	X	X	X	X	X	X	
Company Confidential Inf	ormation																
Neuropathy assessment (FACT/GOG-NTX) (k)		X					X				X					X	
Company Confidential Info																	
Company Confidential Inf	ormation			1		ı	1	1	1	1	ı			1	1		1
IVRS/IWRS	X	X		X	X		X	X	X		X	X	X			X	

ET/EOT=early termination/end of treatment.

⁽a) Subjects can be randomized 24 (+11) days after Screening (between Days -24 and -35). If the elapsed time between the Screening Visit and randomization (Day 1) is greater than allowed, then the eligibility criteria must be reconfirmed before randomization. If the subject fulfils eligibility criteria at randomization, but the visit is postponed because of reasons other than eligibility criteria logistical matters, the subject can be randomized within 7 days after approval of the medical monitor; however, safety laboratory tests must be repeated and the investigator must reconfirm eligibility criteria. If rescreening occurs within one month of the original screening period, then only the following procedures are

required, disease activity parameters (UPCR, anti-dsDNA, urine sediment and complement levels) and safety laboratory tests must be repeated to re-confirm eligibility. Subjects will be randomized once safety laboratory tests and inclusion/exclusion criteria have been reviewed and confirmed by the investigator. Subjects may be rescreened once for urinary sediment, proteinuria or complement levels within 2 weeks of the original Screening Visit.

- CBC with platelet count, chemistries, including liver function tests and urinalysis may be repeated one time to determine eligibility with approval from the medical monitor.
- (b) Informed consent must be signed before any study-specific procedures are performed.
- (c) The Cycle 1, Day 1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (Cycle 1, Day 1). The physical examination must be conducted within 3 days before dosing on Day 1 of each subsequent treatment cycle visit.
- (d) Vital sign measurements are to be made before dosing, when applicable. The blood pressure measurement should be made with the subject in a seated position, after the subject has been sitting quietly for 5 minutes.
- (e) A single 12-lead ECG will be collected at screening to assess eligibility, on Day 1 of each cycle, and at the Final Visit/EOT visit. The ECG may be repeated as clinically indicated during the study at the discretion of the investigator. ECG assessments are to be performed with the subject supine and rested for 5 minutes. When an ECG is scheduled at the same time as blood draws or vital signs then the blood draws and vital signs will take priority and the ECG will be obtained within 1.5 hours before or after the scheduled blood draw/vital sign assessment.
- (f) A blood sample for hematology will be obtained at Screening, Days 1, 8, 15 and 22 of Cycle 1, Days 1, 8, 15, and 22 of Cycle 2 and Cycle 3 before dosing and Day 28/Final Visit of Cycle 3 or ET/EOT visit, and at each Follow Up Visit up to Month 6 from the first dose. Serum chemistry will be obtained at Screening, Days 1, 8, 15 and 22 of each cycle before dosing and Day 28/Final Visit of Cycle 3 or ET/EOT visit, and at each follow up visit up to Month 6 from the first dose. The hematology and chemistry blood samples for Cycle 1, Day 1 may be collected within 4 days before dosing to ensure subject eligibility on study Day 1. If the clinical laboratory testing was performed for screening within 4 days before the Cycle 1, Day 1 dose, it need not be repeated on Cycle 1, Day 1.
- (g) Serum pregnancy test will be performed at Screening. A urine pregnancy test will be performed only for subjects of childbearing potential before each dosing occasion in each cycle, at Final Visit/ET/EOT visits and at each Follow up Visit. The results must be negative within 4 days before the first dose of ixazomib is administered (ie, within the 4 days before Cycle 1, Day 1), or as otherwise required by local regulations. Additional pregnancy testing may be performed during the study at the discretion of the investigator, at the request of an independent ethics committee/institutional review board, or if required by local regulations.
- (h) One blood sample (10.0 mL) will be collected for pharmacogenomic analysis before dosing on study Day 1.
- (i) Blood samples will be collected for RNA analysis during Cycle 1 and Cycle 3.
- (j) Blood samples for ixazomib analysis will be collected on Study Day 1 Cycle 1 predose (within 0.5 hour before dosing) on days 1, 8 and 15. On Day 1 of Cycle 1, sample will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, and 168 (predose Day 8) hours following the first dose. In Cycle 2, samples will be collected predose on Days 1, 8, and 15. Samples will also be collected on Day 22 following first dose in Cycle 2. In Cycle 3 samples will be collected predose on Days 1, 8, and 15. On Day 15 of Cycle 3 following the third dose, samples will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 168 and 312 hours postdose.
- (k) Neuropathy assessment must be performed and evaluated before administration Ixazomib if a dose is scheduled for that visit
- (i) Postmenopausal women by history (ie, last regular menstrual cycle >2 years) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use adequate contraception.
- (m) Samples/procedures will be collected only at the last Follow-up Visit (Month 6). A Follow-up Period of up to 3 months consisting of monthly follow-up visits will start after Cycle 3 to assess any safety issues.
- (n) Company Confidential Information
- (o) Dispense cups for collection of UPCR (three collections to be done prior the visit).
- (p) Collection should occur within 48 hours before visits on the day of dosing of each cycle with results required back to the site before dosing.
- (q) For subjects not moving on to the optional Open-Label Treatment Extension Period.

Appendix A Schedule of Study Procedures: Optional Open-Label Treatment Extension Period

					Open	-Label T	'reatment	Extensi	on Period	I				Follow Up Visit 30 Days after last OL Treatment Cycle
			8-Day Cy low ±2 da				8-Day Cyo low ±2 da				3-Day Cyolow ±2 da		ET /EOT/ Final Visit	
Days	1	8	15	22	1	8	15	22	1	8	15	22	28	
Physical examination (c)	X (c)				X				X				X	X(m)
Concurrent medical conditions	X													
Weight	X				X				X				X	X(m)
Vital signs (d)	X				X				X				X	X
PTE assessment														
AE Assessments	X	X(b)	X(b)		X	X(b)	X(b)		X	X(b)	X(b)		X	X
Monitoring of concomitant medications	X				X				X				X	
Pregnancy avoidance counseling	X	X(b)	X(b)		X	X(b)	X(b)		X	X(b)	X(b)		X	X
Overnight fast													X	X(m)
Study drug dosing	X(a)	X(b)	X(b)		X(a)	X(b)	X(b)		X(a)	X(b)	X(b)			
12-lead ECG (e)	X				X				X				X	
HBsAb and TT antibody titers	X								X				X	X(m)
Hematology (f)	X				X				X				X	X
Chemistry panel (f)	X				X				X				X	X
Lipid panel (fasted):													X	X(m)
Platelets counts white blood cells with differentiation and red blood cells (p)	X				X				X					
Pregnancy test (g)	X				X				X				X	X
Urinalysis (including microscopic analysis)	X				X				X				X	X

Appendix A Schedule of Study Procedures: Optional Open-Label Treatment Extension Period (continued)

				Open	-Label T	reatment	Extension	on Period					Follow Up Visit 30 Days after last OL Treatment Cycle
												ET /EOT/ Final Visit	
1	8	15	22	1	8	15	22	1	8	15	22	28	
X				X				X				X	X
X				X				X				X	X
X				X				X				X	X
X				X				X				X	X(m)
X				X				X				X	X(m)
												X	X
X				X				X				X	X
X				X				X				X	
	V 1 X X X X X X X X X	Visit Wind 1	Visit Window ±2 day 1	X X X X X	Cycles 1 (28-Day Cycle) Cycles Cycles	Cycles 1 (28-Day Cycle) Cycles 2 (28 Visit Window ±2 days Cycles 2 (28 Visit Window ±2 days 1 8 15 22 1 8 X X X X X X X X X X X X X X X X X X X X X X X X X X X X	Cycles 1 (28-Day Cycle) Cycles 2 (28-Day Cyvisit Window ±2 days 1 8 15 22 1 8 15 X X X X X X X X X X X X X X X X X X X X X X X X X X X X X	Cycles 1 (28-Day Cycle) Cycles 2 (28-Day Cycle) Visit Window ±2 days Visit Window ±2 days 1 8 15 22 1 8 15 22 X X X X X X X X X X X X X X X X X X X X X X X X X	Cycles 1 (28-Day Cycle) Cycles 2 (28-D	Visit Window ±2 days Visit Win	Cycles 1 (28-Day Cycle) Cycles 2 (28-Day Cycle) Cycles 3 (28-Day Cycle) Visit Window ±2 days Visit Window ±2 days Visit Window ±2 days 1 8 15 22 1 8 15 X X X X X X X X X X X X X X X X X X X X X X X X X X X X X	Cycles 1 (28-Day Cycle) Cycles 2 (28-Day Cycle) Cycles 3 (28-Day Cycle) Visit Window ±2 days Visit Window ±2 days 1 8 15 22 1 8 15 22 X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X	Cycles 1 (28-Day Cycle) Cycles 2 (28-Day Cycle) Cycles 3 (28-Day Cycle) ET /EOT/ Visit Window ±2 days Visit Window ±2 days Final Visit 1 8 15 22 1 8 15 22 28 X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X <

ET/EOT=early termination/end of treatment.

- (a) First dose of Open-Label treatment cycle administered.
- (b) Call subjects at home to remind about dosing, pregnancy avoidance, and ask about any AEs including symptoms of peripheral neuropathy.
- (c) The physical examination must be conducted within 3 days before dosing on Day 1 of each treatment cycle visit.
- (d) Vital sign measurements are to be made before dosing in each cycle and when applicable. The blood pressure measurement should be made with the subject in a seated position, after the subject has been sitting quietly for 5 minutes.
- (e) The ECG may be repeated as clinically indicated during the study at the discretion of the investigator. ECG assessments are to be performed with the subject supine and rested for 5 minutes. When an ECG is scheduled at the same time as blood draws or vital signs then the blood draws and vital signs will take priority and the ECG will be obtained within 1.5 hours before or after the scheduled blood draw/vital sign assessment.
- (f) If the central laboratory blood test is not available before the first dose of each cycle, a blood sample for hematology will be obtained at the local laboratory and results reviewed before first dose of each cycle, or before each dose if there is a safety concern. Serum chemistry will be obtained Day 1 of each cycle before dosing and Day 28/Final Visit of Cycle 3 or ET/EOT visit, and at the follow up visit. The hematology and chemistry blood samples for Cycle 1, Day 1 may be collected within 7 days before dosing to ensure subject eligibility for open label dosing. If the clinical laboratory testing was performed within 7 days before Cycle 1, Day 1 dose, it need not be repeated.
- (g) A urine pregnancy test will be performed only for subjects of childbearing potential before each dosing occasion in each cycle, at Final Visit/ET/EOT visits and at each Follow

up Visit. The results must be negative within 4 days before the first dose of ixazomib is administered (ie, within the 4 days before Cycle 1, Day 1), or as otherwise required by local regulations. Additional pregnancy testing may be performed during the study at the discretion of the investigator, at the request of an independent ethics committee/institutional review board, or if required by local regulations.

(k) Neuropathy assessment must be performed and evaluated before administration of ixazomib.

- (m) Samples/procedures will be collected only at the last Follow-up Visit.
- (o) Dispense cups for collection of UPCR (3 collections to be done prior the visit).
 (p) Collection should occur within 48 hours before visits on the day of dosing of each cycle with results required back to the site before dosing.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

- 1. Conduct the study in accordance with the protocol.
- 2. Personally conduct or supervise the staff who will assist in the protocol.
- 3. Ensure that study related procedures; including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
- 4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
- 5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations Part 56, ICH, and local regulatory requirements.
- 6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
- 7. Ensure that requirements for informed consent, as outlined in 21 Code of Federal Regulations Part 50, ICH and local regulations, are met.
- 8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
- 9. Prepare and maintain adequate case histories of all persons entered into the study, including (e)CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
- 10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents

- 11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs and return all unused sponsor-supplied drugs to the sponsor.
- 12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

- 1. A statement that the study involves research.
- 2. An explanation of the purposes of the research.
- 3. The expected duration of the subject's participation.
- 4. A description of the procedures to be followed, including invasive procedures.
- 5. The identification of any procedures that are experimental.
- 6. The estimated number of subjects involved in the study.
- 7. A description of the subject's responsibilities.
- 8. A description of the conduct of the study.
- 9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
- 10. A description of the possible side effects of the treatment that the subject may receive.
- 11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- 12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this
- 13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
- 14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- 15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
- 16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
- 17. The anticipated expenses, if any, to the subject for participating in the study.
- 18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
- 19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may

- discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- 20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- 21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
- 22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
- 23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
- 24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
 - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
 - e) that the subject's identity will remain confidential in the event that study results are published.

- 25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening through 90 days after the last dose of trial treatment. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued.
- 26. Male subjects must use adequate contraception (as defined in the informed consent) from Screening through 90 days after the last dose of trial treatment.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

						D ₄ = 1	Cycle	1					Day 0	Da 15
Time poi		e-	15 min (± 5 min)	30 min (± 5 min)	1 h (± 1 min	.5 (±	15 (±		4 hr (± 45 min)	8 hr (± 1 hr)	24 (± 1	hr	Day 8 168 hr (± 8 hr)	Day 15 Pre- dose
Plasma P blood dra	K X		X	X	X			X	X	X	X		X (a)	X (a)
Company	Confide	ntial Ir	nformatio	on										
RNA	X	(a)			X			X	X	X	X	ζ		
Serum biomarke	ers	(a)									X	ζ	X	
Urine Biomarke	ers	(a)									X	ζ	X	
							Cycle	2						
Time p (wind			Da	ay 1			Day 8			Day	15		Day 22	
Plasma blood			X	(a)	X (a)					X (a)		X	
	y Confid	ential	Informa	tion										
		ential	Informa	tion			Cycle	3						
	y Confid	ential		tion			Cycle Day 15				I	Day 16	Day 22	Day 28
	y Confid		e	15 min (± 5 min)	30 min (± 5 min)	1 hr (± 15 min)			(±	45 (±		Day 16 24 hr (± 2 hr)	168 hr	312 hr
Plasma PK blood draw	P Day 1 X (a)	Day 8 X (a)	Day 15 X (a)	15 min (± 5 min)	(± 5	(± 15	Day 15 1.5 hr (± 15	(b) 2 hr (± 15	(± mi	45 (± in)	hr : 1	24 hr (± 2		312 hr
Plasma PK blood	P Day 1 X (a)	Day 8 X (a)	Day 15 X (a)	15 min (± 5 min)	(± 5 min)	(± 15 min)	Day 15 1.5 hr (± 15 min)	(b) 2 hr (± 15 min)	(± mi	45 (± in)	hr : 1 r)	24 hr (± 2 hr)	168 hr (± 8 hr)	312 hr (± 8 hr
Plasma PK blood draw	P Day 1 X (a)	Day 8 X (a)	Day 15 X (a)	15 min (± 5 min)	(± 5 min)	(± 15 min)	Day 15 1.5 hr (± 15 min)	(b) 2 hr (± 15 min)	(± mi	45 (± in)	hr : 1 r)	24 hr (± 2 hr)	168 hr (± 8 hr)	312 hr (± 8 hr
Plasma PK blood draw	P Day 1 X (a)	Day 8 X (a)	Day 15 X (a)	15 min (± 5 min)	(± 5 min)	(± 15 min) X	Day 15 1.5 hr (± 15 min)	(b) 2 hr (± 15 min) X	(± mi	45 (± in)	hr : 1 r)	24 hr (± 2 hr)	168 hr (± 8 hr)	

EOC = end of cycle.

⁽a) Predose within 0.5 hour before dosing.

⁽b) Sampling times referenced as time post third dose of Cycle 3.

Collection, Storage, and Shipment of Bioanalytical Samples PK Ixazomib Analysis Instructions for Processing of Plasma Samples for Bioanalytical Analysis of ixazomib

- 1. Collect 3 mL of venous blood into a chilled Becton-Dickinson Vacutainer. All ixazomib blood samples should be collected into lavender topped vacutainers containing K₂EDTA.
- 2. Gently invert the vacutainer 8 to 10 times to mix the additive with the collected blood before centrifugation and place immediately on ice.
- 3. Within 15 minutes place vacutainers into centrifuge for 10 minutes at approximately 1000 to 1300 relative centrifugal force (RCF). Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
- 4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, add exactly 0.5000 mL of plasma to 2 vials containing a designated amount of lyophilized critic acid (250 mg). Vortex the vials after capping. Discard the remaining plasma following appropriate biohazard procedures. Labeling may include protocol number (MLN9708-101), sample matrix (ie, plasma), analyte (ixazomib), randomization sequence number, cycle, profile day (ie, Profile Day 1) and scheduled time points, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).

NOTE: If <0.5 mL plasma is obtained post centrifugation, do not process or store split1 or split2, record split1: ISV (insufficient sample volume), split2:ISV. If <1.0 mL plasma is obtained post centrifugation, process and store split1 according to procedure; do not process or store split2, record split 2:ISV. Discard remaining plasma using appropriate biohazard waste disposal procedures. Replace cap on tube and freeze the samples immediately at -20°C or -70°C.

5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C (for no longer than 25 days) or -70°C until shipment to PPD Global Central Lab per the instructions in their laboratory manual. PPD Labs will further ship samples to Tandem, New Jersey for analysis. No more than 60 minutes will elapse between blood collection and freezing the plasma sample.

	y Confidential Information	
1.	mpany Confidential Information	
2.		
3.		



Shipping of Plasma Samples for Bioanalytical Analysis of Ixazomib

- 1. Biological samples (ie, plasma) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days before a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
- 2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
- 3. Separate the duplicate SET 2 samples from the SET 1 samples.
- 4. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc®) containing additional absorbent material.
- 5. Using a permanent marker, write the 4-digit randomization sequence number, sample matrix (ie, plasma), analyte (ixazomib), number of samples, and "SET 1" on each self-sealing bag.
- 6. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."
- 7. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study drug (ixazomib), protocol number (MLN9708-101), investigator's name, sample type (ie, plasma), randomization sequence number, cycle, profile day and scheduled time point, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
- 8. For sample packing, use dry ice generously (eg, 20 25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
- 9. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the styrofoam container. Place the lid on the styrofoam container and seal completely with

strapping tape. Place the styrofoam container in a cardboard shipping carton and seal securely with strapping tape.

- 10. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
- 11. Affix the appropriate address label to each shipping carton and ship to Global Central Lab per the instructions in their laboratory manual.

Appendix F Total Blood Volume of Blood Withdrawal

						llected (m nd Treatm			
)ay	-24(-11) to -1	1			<u>ouble-Bill</u> 8		1ent) 5	22	Total (mL
ample Type	-24(-11) t0 -1	1				1	3	22	Total (IIIL
afety laboratory samples	22	23 (b) (f)			13(b) (f	23 (o) (f)	10	91
Plasma PK samples	22	24 (a)	3		3 (a,b)	3		10	33
Company Confidential Informa	ation	24 (a)	3		3 (a,0)	3 1	(υ)		33
Serum biomarkers	1011	3 (b)	3		3				9
DNA sample		10	3						10
RNA samples		12.5	2.5	-					15
ANA samples		12.3	2.5	,					13
	Total Blood	Volume for	Screenin	g and	in Cycle	1			170
				2 (D)	11 511	1.75	0		I
			Cycle		uble-Bline	l Treatme	nt)		
Day		1		8		15		22	Total (mL
Sample Type									
Safety laboratory sampl		20		13 (f)		23 (f)		10	66
Plasma PK sample		3 (b)		3 (b)		3 (b)		3	12
Company Confidential Inform	nation								
				~ .					
	10	tal Blood V	olume in (Cycle	2				80
			Cyclo	3 (Doi	uhla Blina	l Treatme	nt)		
Day		1	8		15	16	22	28	Total (mL
Sample Type		1	<u> </u>		13	10		20	1 Otal (IIIL
Safety laboratory sampl	as (b)	24	13 (f)	2.	3 (f)		10	20	90
		3 (b)	3 (b)		4 (c)	3	3	3	39
Plasma PK sample Company Confidential Informa	ation	3 (0)	3 (0)		+ (0)	3		3	39
RNA samples	İ					i		2.5	2.5
KIVA samples								2.3	2.3
			Tota	ıl Rloo	d Volum	e in Cycle	3		143.5
			100	ii Dioo	d volulli	in Cycle			140.0
		Foll	ow-up Per	riod (d	l) (No Op	en Label T	reatm	ient)	Total (mL)
Month		Month		(Month			Month 6	,
Sample Type									
Safety laboratory sam	ples	20			20			20	60
J J	,								
	Total Bloo	od Volume	in the Foll	low-up	Period				60
						d and Fol			Total (mL)
		Cycle 1	Cycle 2		Cycle 3	ET/EOT		Follow-up	
0.0.11		20.42.42	20(1) (2		0.41.40	Visi	t	visit	100
Safety laboratory sam		20 (b) (f)	20(b) (f)		0 (b) (f)	20		20	100
	Total Blo	od Volume i	in the Foll	low-up	Period				100
						. ~ -			4.5
Total Approximate Blood	Volume (mL)		-	duratio	on collect	ed per Sul	oject (r	10 open label	453.5
\D		trea	tment)						
									1
DR Γotal Approximate Blood V	· • · · · · · · · · · · · · · · · · · ·		, , ,		11 /				493.5

Direct venipuncture is the only acceptable method of blood collection.

- (a) Plasma PK samples collected in Cycle 1 on Day 1: Predose (within 0.5 hour before dosing) on Days 1, 8 and 15. On Day 1 of Cycle 1, following the first dose, sample will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, and 168 (predose Day 8) hours postdose. (b) Predose.
- (c) Plasma PK samples collected in Cycle 3 Predose (within 0.5 hour before dosing) on study Days 1, 8, and 15. On Day 15 of Cycle 3 following the third dose, samples will be collected at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 168 and 312 hours postdose in Cycle 3. (d) Follow-up visits on Days 112, 140, and 168.
- (e) Company Confidential Information
- (f) Collection should occur within 48 hours before visits on the day of dosing of each cycle with results required back to the site before dosing.
- (g) Open Label Treatment Period and Follow-up consists of up to 3 additional cycles of treatment (Day 85 to 168) with a Follow-up visit 30 days after the last dosing.

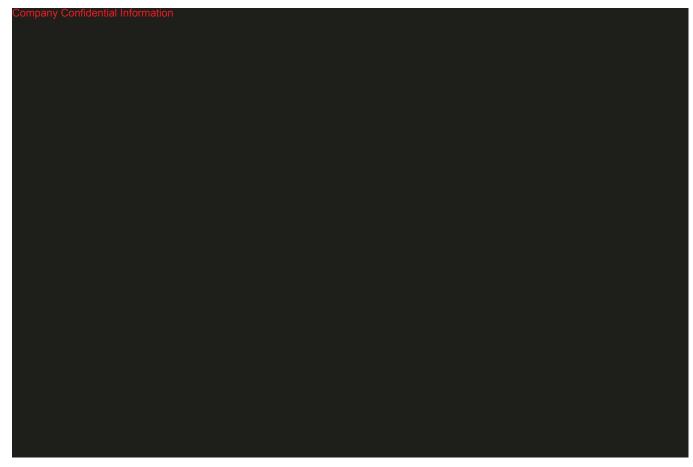
Appendix G Instructions for Processing and Shipping of Plasma Samples for Pharmacogenomics

DNA Sample Collection

•	Company Confidential Inform	nation		

RNA Sample Collection

•	Company Confidential Information
•	



Sample Shipment

- Ship samples only on Monday, Tuesday, or Wednesday, and at least 2 days before a national holiday, to minimize the possibility of samples in transit over a weekend or holiday. The laboratory must confirm arrival of the shipped samples.
- Company Confidential Information
- For shipment and /or storage longer than 5 calendar days, samples should be frozen at -20°C until shipment. Samples must be shipped frozen on dry ice to the central laboratory for processing.
- Before shipping, ensure the sample tubes are tightly sealed.
 RNA samples may be shipped to additional testing facility for transcriptional analysis.

Sample Storage

The sponsor designated long term storage provider will store the PGx samples in a secure storage space with adequate measures to protect confidentiality. The sponsor designated long term storage provider has validated procedures in place for transport, delivery, retention, retrieval, and destruction of the specimens. The samples will be retained while research on study drug/ disease state continues for up to but no longer than 15 years or as required by applicable law.

Appendix H Criteria for Classification of Systemic Lupus Erythematosus

The 1982 Revised American College of Rheumatology (ACR) Criteria for Classification of Systemic Lupus Erythematosus.

1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritisconvincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion
	OR
	2. Pericarditisdocumented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria >0.5 grams per day or >than 3+ if quantitation not performed
	OR
	2. Cellular castsmay be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizuresin the absence of offending drugs or known metabolic derangements; eg, uremia, ketoacidosis, or electrolyte imbalance
	OR
	2. Psychosisin the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis, or electrolyte imbalance

9. Hematologic Disorder	1. Hemolytic anemiawith reticulocytosis
	OR
	2.Leukopenia<4,000/mm³ on ≥2 occasions
	OR
	3. Lymphopenia<1,500/ mm³ on ≥2 occasions
	OR
	4. Thrombocytopenia<100,000/ mm³ in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer
	OR
	2. Anti-Sm: presence of antibody to Sm nuclear antigen
	OR
	3. Positive finding of antiphospholipid antibodies on:
	a) an abnormal serum level of IgG or IgM anticardiolipin antibodies,
	b) a positive test result for lupus anticoagulant using a standard method, or
	c) a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Company Confidential Information	Company Confidential Information

The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

The 2012 Systemic Lupus International Collaborating Clinics (SLICC) Criteria for Classification of Systemic Lupus Erythematosus

Clinical criteria

- 1. Acute cutaneous lupus, including:
 - Lupus malar rash (do not count if malar discoid).
 - Bullous lupus.
 - Toxic epidermal necrolysis variant of SLE.
 - Maculopapular lupus rash.
 - Photosensitive lupus rash.

in the absence of dermatomyositis

- OR subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias).
- 2. Chronic cutaneous lupus, including:
 - Classic discoid rash.
 - Localized (above the neck).
 - Generalized (above and below the neck).
 - Hypertrophic (verrucous) lupus.
 - Lupus panniculitis (profundus).
 - Mucosal lupus.
 - Lupus erythematosus tumidus.
 - Chillblains lupus.
 - Discoid lupus/lichen planus overlap.
- 3 Oral ulcers
 - Palate.
 - Buccal.
 - Tongue.
 - OR nasal ulcers

in the absence of other causes, such as vasculitis, Behçet's disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis, and acidic foods

- 4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs). in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia
- 5. Synovitis involving 2 or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness.
- 6. Serositis.
 - Typical pleurisy for more than 1 day.
 - OR pleural effusions.
 - OR pleural rub.
 - Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day.
 - OR pericardial effusion.
 - OR pericardial rub.
 - OR pericarditis by electrocardiography.

in the absence of other causes, such as infection, uremia, and Dressler's pericarditis

7. Renal.

- Urine protein—to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours.
- OR red blood cell casts.
- 8. Neurologic.
 - Seizures.
 - Psychosis.
 - Mononeuritis multiplex.

in the absence of other known causes such as primary vasculitis

- Myelitis.
- Peripheral or cranial neuropathy.

in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus

Acute confusional state.

in the absence of other causes, including toxic/metabolic, uremia, drugs

9. Hemolytic anemia.

10. Leukopenia (<4,000/mm³ at least once).

in the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension

OR

Lymphopenia (<1,000/mm³ at least once)

in the absence of other known causes such as corticosteroids, drugs, and infection

11. Thrombocytopenia (<100,000/mm³) at least once.

in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura

Immunologic criteria

- Company Confidential Information
- 2. Anti-dsDNA antibody level above laboratory reference range (or >2-fold the reference range if tested by ELISA).
- 3. Anti-Sm: presence of antibody to Sm nuclear antigen.
- 4. Antiphospholipid antibody positivity as determined by any of the following:
 - Positive test result for lupus anticoagulant.
 - False-positive test result for rapid plasma reagin.
 - Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM).
 - Positive test result for anti–β2-glycoprotein I (IgA, IgG, or IgM).
- 5. Low complement.
 - Low C3.
 - Low C4.
 - Low CH50.
- 6. Direct Coombs' test in the absence of hemolytic anemia.

Criteria are cumulative and need not to be present concurrently

Requirements to classify a patient as having $SLE: \ge 4$ criteria (at least 1 clinical criterion and 1 laboratory criterion) OR biopsy-proven nephritis compatible with SLE in the presence of ANA or anti- dsDNA antibodies.

Appendix I Pathology Classification of LN

International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis:

Class I - Minimal mesangial lupus nephritis

Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence

Class II - Mesangial proliferative lupus nephritis

Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits

May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy

Class III - Focal lupus nephritis

Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations

Class IV - Diffuse lupus nephritis

Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving $\geq 50\%$ of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when $\geq 50\%$ of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when $\geq 50\%$ of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation

- Class IV-S (A): Active lesions: diffuse segmental proliferative lupus nephritis.
- Class IV-G (A): Active lesions: diffuse global proliferative lupus nephritis.
- Class IV-S (A/C): Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis.
- Class IV-G (A/C): Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis.
- Class IV-S (C): Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis.
- Class IV-G (C) Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis.

Class V: Membranous lupus nephritis

- Pure membranous glomerulonephritis.
- Associated with lesions of class II.

- Associated with lesions of class III.
- Associated with lesions of class IV.

Class VI Advanced sclerosing glomerulonephritis

WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF LUPUS

NEPHRITIS (modified in 1982)

Class I Normal glomeruli	a. Nil (by all techniques)
	b. Normal by light microscopy, but deposits by electron or immunofluorescence microscopy
Class II Pure mesangial alterations (mesangiopathy)	a. Mesangial widening and/or mild hypercellularity (+)
	b. Moderate hypercellularity (++)
Class III Focal Segmental glomerulonephritis	a. With "active" necrotizing lesions
(associated with mild or moderate mesangial alterations)	b. With "active" and sclerosing lesions
anterations)	c. With sclerosing lesions
Class IV Diffuse glomerulonephritis (severe	a. Without segmental lesions
mesangial, endocapillary or mesangio-capillary proliferation and/or extensive subendothelial	b. With "active" necrotizing lesions
deposits	c. With "active" and sclerosing lesions
	d. With sclerosing lesions
Class V Diffuse membranous	a. Pure membranous glomerulonephritis
glomerulonephritis	b. Associated with lesions of class II
	c. Associated with lesions of class III
	d. Associated with lesions of class IV
Class VI	Advanced sclerosing glomerulonephritis

Appendix J Diagnostic Criteria for Psychoactive Substance Dependence

The following is taken from DSM-IV:

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by 3 (or more) of the following, occurring at any time in the same 12-month period:

- 1. Tolerance, as defined by either of the following:
 - A need for markedly increased amounts of the substance to achieve intoxication or desired effect,
 - Markedly diminished effect with continued use of the same amount of the substance.
- 2. Withdrawal, as manifested by either of the following:
 - The characteristic withdrawal syndrome for the substance,
 - The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
- 3. The substance is often taken in larger amounts or over a longer period than was intended.
- 4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
- 5. A great deal of time is spent in activities necessary to obtain the substance (eg, visiting multiple doctors or driving long distances), use the substance (eg, chainsmoking) or recover from its effects.
- 6. Important social, occupational or recreational activities are given up or reduced because of substance use
- 7. The substance use is continued despite knowledge of having a persistent or recurring physical or psychological problem that is likely to have been caused or exacerbated by the substance (eg, current cocaine use despite recognition of cocaine-induce depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption.
 - Criteria for Severity of Psychoactive Substance Dependence.
 - Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.
 - Moderate: Symptoms or functional impairment between "mild" and "severe".
 - Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.
 - In Partial Remission: During the past six months, some use of the substance and some symptoms of dependence.

• In Full Remission: During the past six months, either no use of the substance, or use of the substance and no symptoms of dependence.

Diagnostic Criteria for Psychoactive Substance Abuse

- 1. A maladaptive pattern of psychoactive substance use, leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring at any time in the same 12-month period:
 - a) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (eg, repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school, neglect of children or household).
 - b) Recurrent substance use in situations in which it is physically hazardous (eg, driving an automobile or operating a machine when impaired by substance use).
 - c) Recurrent substance-related legal problems (eg, arrests for substance-related disorderly conduct).
 - d) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (eg, arguments with spouse about consequences of intoxication, physical fights).
- 2. The symptoms have never met the criteria for substance dependence for this class of substance

Appendix K Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 11.

Change 1: Updated the drug metabolism and concomitant medication information to reflect recent population pharmacokinetic (PK) analyses and drug-drug interaction study results from an ixazomib study (Study C16009) demonstrating that cytochrome P-450 inhibitors do not affect ixazomib PK and clarified details about PK assessments.

The primary change occurs in Section 4.1.4.2 Drug Metabolism and PK

Initial wording:

Ixazomib citrate is hydrolyzed to the boronic acid form ixazomib which is mainly cleared via metabolism; clinical PK data indicate that renal clearance contributes little to the total elimination of ixazomib (<10% is renally cleared following intravenous administration). Consistently, no relationship between creatinine clearance (CrCl) and renal clearance has been observed in the preliminary population PK analysis (N=137) over a wide range of renal function categories (CrCl range: 22-236 mL/min). Therefore, it is expected that there will be no increases in ixazomib exposures when administered to subjects with mild to moderate renal impairment. In vitro studies show that ixazomib is metabolized by multiple cytochrome P450 (CYP) enzymes and non-CYP enzymes/proteins. Ixazomib is not an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. Prednisone and MMF treatment is allowed in this study. Prednisone is metabolized via CYP3A4 and is a known inducer of CYP 2C19, MMFs major metabolic pathway is mediated via glucuronosyltransferases therefore the likelihood of a drug interaction with ixazomib in both cases is considered to be low. Overall, the potential for ixazomib treatment to produce drug-drug interactions (DDIs) via CYP inhibition is inferred to be low. In study C16009 coadministration of ixazomib with ketoconazole caused an increase of ~ 2-fold in area under the plasma concentrationtime curve from 0 to 264 hours (range 1.9-2.3). In contrast, C_{max} values were similar with and without ketoconazole, the mechanism of the interaction appears to be a decrease in the systemic clearance of ixazomib as opposed to an increase in oral bioavailability, therefore strong 3A4 inhibitors are excluded co-medications in this study (see Section 7.3).

Amended or new wording:

Ixazomib citrate is hydrolyzed to the boronic acid form ixazomib which is mainly cleared via metabolism; clinical PK data indicate that renal clearance contributes little to the total elimination of ixazomib (≤10% is renally cleared following intravenous administration). Consistently, no relationship between creatinine clearance (CrCl) and renalsystemic clearance has been observed in the preliminary population PK analysis (N=137) over a wide range of renal function categories (CrCl range: 22-236 mL/min). Therefore, it is expected that there will be no increases in ixazomib exposures when administered to subjects with mild to moderate renal impairment [21, 22].

In vitro studies showindicate that ixazomib is metabolized by multiple evtechrome P450 (CYP) enzymesCYPs and non-CYP enzymes/proteins. Ixazomib is not an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4, nor is itAt clinically relevant concentrations of ixazomib, in vitro studies using human complementary DNAexpressed CYP isozymes showed that no specific CYP isozyme predominantly contributes to ixazomib clearance. At concentrations exceeding those observed clinically (10 µM), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%) and 2C9 (<1%). In contrast, at 0.1 μM and 0.5 µM substrate concentrations, which are closer to clinical concentrations of ixazomib, non-CYP-mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, minimal CYP-mediated drug-drug interactions (DDIs) with a selective CYP inhibitor would be expected. In addition, ixazomib is neither a reversible nor a time-dependent inhibitor of **CYPCYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or** 3A4/5. Prednisone and MMF treatment is allowed in this study. Prednisone is metabolized via CYP3A4 and is a known inducer of CYP 2C19, MMFs major metabolic pathway is mediated via glucuronosyltransferases; therefore, the likelihood of a drug interaction with ixazomib in both cases is considered to be low. Overall, the potential for ixazomib treatment to produce DDIs via CYP inhibition is inferred to be low.

In study C16009 coadministration of ixazomib with ketoconazole caused an increase of ~ 2-fold in AUC(0-264) (range 1.9-2.3). In contrast, Cmax values were similar with and without ketoconazole, the mechanism of the interaction appears to be a decrease in the systemic clearance of ixazomib as opposed to an increase in oral bioavailability, therefore strong 3A4 inhibitors are excluded co-medications in this study (see Section 7.3), a phase 1 DDI study, the PK of ixazomib was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor (Study C16009, Arm 5); hence, no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors [21]. These findings are explained by the in vitro metabolism data indicating the lack of a discernible contribution of CYP-mediated metabolism at clinically relevant ixazomib concentrations. As discussed earlier, no CYP isoforms have been identified to contribute meaningfully to ixazomib metabolism at clinically relevant concentrations and CYP3A contribution to total metabolism was highest across all CYP isoforms when characterized at a supratherapeutic concentration of 10 µM. Therefore, based on the totality of information from the clinical clarithromycin DDI study and the in vitro CYP phenotyping data, it can be concluded that ixazomib PK is not likely to be altered upon co-administration with any CYP isoform-selective inhibitor, including strong CYP1A2 inhibitors. Consistently in the population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance [22]. Therefore, no dose

adjustment is required for patients receiving strong inhibitors of CYP1A2.

In a phase 1 DDI study, coadministration of ixazomib with rifampin decreased ixazomib C_{max} by 54% and area under the plasma concentration-time curve by 74% (Study C16009, Arm 4) [21]. Accordingly, concomitant administration of ixazomib with strong CYP3A inducers should be avoided (see Section 7.3). Please refer to the prescribing information for ixazomib for further details [23].

Rationale for Change:

To reflect updated information regarding drug metabolism and DDIs for ixazomib as per the United States Prescribing Information and EU SmPC.

The following sections also contain this change:

7.3 Excluded and Restricted Medications, Procedures and Dietary Products

16.0 REFERENCES

Change 2: Added optional Open-Label Treatment Extension Period to the Study Design to allow treatment with up to 3 additional cycles of ixazomib at the discretion of the investigator.

The primary change occurs in Section 6.1 Study Design

Initial wording:

This study is a phase 1b, randomized, double-blind, placebo-controlled, safety, tolerability, and PK study of MRD of ixazomib for the treatment of subjects with ISN / RPS Class III, IV, V or V changes [excluding Class III (C), IV-S (C) and IV-G (C)] or WHO 1982 classification of Class III, IV or V (excluding Class IIIc and IVd). It is anticipated that 4 ixazomib dose levels will be examined.

At least 5 subjects (4:1) will be recruited into the 0.5 mg dose group (Cohort A), at least 5 subjects (4:1) in the 2.0 mg dose group (Cohort B), 8 subjects (6:2) in the 3.0 mg dose group (Cohort C), and 8 subjects (6:2) in the 4.0 mg dose group (Cohort D). Subjects will be considered eligible on the basis of study inclusion and exclusion criteria, verified by an independent adjudication committee, and randomized. Following each of the 0.5, 2.0, and 3.0 mg dose cohorts, available PK and safety data will be evaluated prior to escalation. For each dose level cohort, the SRC will carefully review the available blinded safety, tolerability, and PK data to determine if dosing should be escalated in the next cohort, lowered or expanded within the same dose cohort to obtain additional information prior to a dose-escalation decision, or stopped. After 5 subjects are recruited in the 4.0 mg dose group (Cohort D) and complete at least 1 cycle of ixazomib or placebo, an analysis will be conducted on available PK data and blinded safety data from all cohorts. Subject numbers may be increased as appropriate per cohort for a total number not exceeding 40 subjects in all cohorts combined. Two subjects with Class V or Class II with Class V lupus nephritis are permitted per cohort. Subjects will be treated with three 28-day cycles of ixazomib or placebo.

Each 28 day cycle will consist of 3 once-weekly oral doses of 0.5, 2.0, 3.0, or 4.0 mg of ixazomib (dosage strength is stated as the active boronic acid ixazomib) or placebo, depending on the cohort. Subjects who received a dose <2.0 mg and completed all cycles including the Follow-up Period, will be permitted to re-enroll into the 2.0 and 3.0 mg dose groups, provided they have no drug-related adverse events >Grade 1, no adverse events >Grade 2, continue to meet all inclusion and exclusion criteria, and the SRC (consisting of sponsor personnel and the coordinating investigator) have reviewed and approved enrollment. Subjects must be receiving standard of care treatment for LN and remain on their current stable and allowed therapies during the screening period and throughout the duration of the study (Section 8.1.1.2).

Subjects can be randomized on Day 1, 24 days after first screening visit (between day -24 and -35) and once safety laboratory tests and inclusion/exclusion criteria have been reviewed and confirmed by the investigator. If the elapsed time between the Screening Visit and Randomization (Day 1) is greater than the allowed screening period, then the eligibility criteria must be re-confirmed in a second screening visit prior to randomization. Disease activity parameters (eg, UPCR, anti-dsDNA, urine sediment and/or complement levels) and safety laboratory tests (hematology and chemistry panel) must be repeated to re-confirm eligibility.

The study consists of the following Periods: a Screening Period (up to 35 days), a Treatment Period (Day 1 to Day 84) and a Follow-up Period (Day 85 to Day 168). Subjects can be randomized 24 (+11) days after Screening (between Days -24 and -35) and once safety laboratory tests and inclusion/exclusion criteria have been reviewed and confirmed by the investigator. Diagnostic criteria, disease activity measures, and treatment history will be documented, and required laboratory investigations initiated. Subject eligibility will be reviewed by an adjudication committee. The responsibilities and criteria of this committee will be defined in an adjudication charter.

Following verification of eligibility, subjects will return to the clinic on Day 1, undergo baseline assessments, laboratory testing, and will be randomized to either ixazomib or placebo within each cohort/dose level. The Treatment Period consists of three 28-day treatment cycles (Cycles 1, 2, and 3) without intra-subject dose escalation. Subjects will receive ixazomib consisting of drug administration on Days 1, 8, and 15 of each 28-day cycle. The second and third cycle will commence on the first day following Day 28 of the preceding cycle (ie, with a period of 13 days between the third drug administration of a cycle and the first drug administration of the following cycle). The treatment period will be limited to 3 complete cycles with ixazomib, with an expected duration of 12 weeks. However, the total treatment period may be longer than the standard 12 weeks if delays between cycles are necessary due to adverse events. After completion of Cycle 3, the subject will enter the Follow-up Period. A Follow-up Period of up to 3 months, consisting of monthly follow-up visits, will start after the end of the Treatment Period (Day 84) to assess

any safety issues.

Subjects will receive ixazomib cycles consisting of doses of 0.5 mg (Cohort A), 2 mg (Cohort B), 3 mg (Cohort C), and 4 mg (Cohort D) or placebo. The ascending dose cohorts will be enrolled sequentially. Dosing of subsequent cohorts will not commence until at least 5 subjects in Cohorts A and B and 8 subjects in Cohort C have received at least 1 dose of investigational drug and have reached Day 28 of Cycle 1 or have completed their last evaluation within Cycle 1 with a satisfactory review of all available safety and tolerability data. Subjects discontinued or withdrawn after randomization for nonsafety reasons will only be replaced if the number of subjects per cohort evaluable for safety on Day 28 of Cycle 1 is reduced below 6 subjects for Cohorts C and D, below 5 subjects for lower than 3.0 mg dose cohorts, or the SRC recommends expanding with the same dose to obtain additional information prior to a dose-escalation decision. Down-titration of ixazomib is permitted for individual subjects for safety and tolerability reasons at any time during the Treatment Period, except for subjects receiving 0.5 mg in Cohort A. If necessary for safety or tolerability reasons or in the judgment of the investigator, ixazomib treatment should be stopped altogether, and an End of Study Visit should be completed. The subject should then complete the remainder of the study period as the Follow-up Period. Dose modification and dose deferral should be discussed with the Sponsor's Medical Monitor; guidelines for the modification or deferral of doses will be provided.

During the Double-Blind Treatment Period ixazomib will always be dosed at the study site and subjects will return to the clinic for each administration of ixazomib. For scheduling flexibility, study visits can occur ± 2 days from each scheduled day during the Treatment Period and ± 1 week during the Follow-Up Period. A minimum of 120 hours should occur between ixazomib doses. Any variances in the dosing schedule should not alter the schedule of subsequent dosing.

Subjects will undergo safety laboratory assessments, total IgG/IgM/IgA, LN assessments including but not limited to UPCR, eGFR anti-dsDNA antibodies, and complement C3 and C4 levels via a central laboratory according to the Schedule in Appendix A. Pharmacogenomic (PGx) and exploratory biomarker samples will also be sent to a central lab for analysis.

Ixazomib is an investigational, orally bioavailable 20S proteasome inhibitor with an estimated terminal elimination half-life of ~ 4 to 9 days in plasma. For Cohorts A to D, plasma concentrations of ixazomib over time will be evaluated following the first dose of Cycle 1 and the last dose of Cycle 3. Predose samples will be collected before each dose in Cycles 1, 2, and 3. Available PK data will be reviewed as part of the overall safety and tolerability evaluation of ixazomib in LN and for the dose escalation decision.

Recent evidence suggests that genetic variation accounts for differing responses to bortezomib therapy. A single nucleotide polymorphism (SNP) at position 11 in the

PSMB1 gene (in the region encoding the leader sequence for the beta subunit of the 20S proteasome) has been associated with reduced proteasome activity and is associated with enhanced bortezomib activity in multiple myeloma and relapsed follicular lymphoma. Company Confidential Information

In addition, hematology and chemistry safety lab assessments will be collected prior to each dose of ixazomib; the results of all available laboratory tests will be reviewed by the Investigator prior to administration of the scheduled dose of ixazomib. A negative urine pregnancy testing is required prior to administration of investigational drug.

In common with other immunosuppressant and cytotoxic agents, ixazomib may have additional effects on host defense. The subject's immunization status should be reviewed at the Screening Visit, and all appropriate vaccinations should be completed at least 1 month prior to Treatment. These may include but are not limited to pneumococcal and inactivated influenza vaccines.

If lymphopenia is noted after treatment with ixazomib, subjects may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster, herpes simplex viruses and cytomegalovirus. Antiviral therapy such as acyclovir or valacyclovir may be initiated at the onset of infection. Other antivirals are also acceptable. Provision of medication will be arranged by the Investigator from local suppliers and will be reimbursed by the Sponsor.

In oncology studies with ixazomib GI issues, rash and peripheral neuropathy occurred in some subjects. GI effects included diarrhea, nausea and vomiting and to minimize the risk of GI toxicities, subjects with LN should skip dosing with their immunosuppressant drug (eg, MMF) on days of dosing with ixazomib. Peripheral neuropathy will be monitored using the FACT/GOG-NTX neuropathy assessment before the start of each cycle. See Section 10.1.5 for management of AEs of special interest.

Although renal adverse events have been rare in studies with oncology subjects, dehydration due to GI toxicity, concomitant medications and disease progression could contribute to renal dysfunction. Chemistry laboratory parameters including serum creatinine (sCr) will be monitored weekly and treatment discontinued if a decrease >25% in estimated glomerular filtration rate (eGFR) or doubling in sCr from baseline is observed (see Section 7.4.3).

Each Investigator will review any safety findings and laboratory results to determine

if a subject should receive the next dose within each cycle. The investigator will evaluate safety and tolerability for each subject on Day -1 and prior to each dose during every cycle, as shown in study schematic (Figure 6.a) below. On Day 22 of each cycle, the investigator-led team will evaluate all available safety information for the subject.

Amended or new wording:

This study is a phase 1b, randomized, double-blind, placebo-controlled, safety, tolerability, and PK study of MRD of ixazomib for the treatment of subjects with ISN/RPS Class III, IV, V or V changes [excluding Class III (C), IV-S (C), and IV-G (C)] or WHO 1982 classification of Class III, IV, or V (excluding Class IIIc and IVd) LN. It is anticipated that 4 ixazomib dose levels will be examined. At least 5 subjects (4:1) will be recruited into the 0.5 mg dose group (Cohort A), at least 5 subjects (4:1) in the 2.0 mg dose group (Cohort B), 8 subjects (6:2) in the 3.0 mg dose group (Cohort C), and 8 subjects (6:2) in the 4.0 mg dose group (Cohort D). Subjects will be considered eligible on the basis of study inclusion and exclusion criteria, verified by an-independent adjudication committee, and randomized. Following each of the 0.5, 2.0, and 3.0 mg dose cohorts, available PK and safety data will be evaluated before escalation. For each dose level cohort, the SRC will carefully review the available blinded safety, tolerability, and PK data to determine if dosing should be escalated in the next cohort, lowered, or expanded within the same dose cohort to obtain additional information before a dose-escalation decision, or stopped. After 5 subjects are recruited in the 4.0 mg dose group (Cohort D) and complete at least 1 cycle of ixazomib or placebo, an analysis willmay be conducted on available PK data and blinded safety/tolerability data from all cohorts. Subject numbers may be increased as appropriate per cohort forto a total number not exceeding to exceed 40 subjects in all cohorts combined. Two subjects with Class V or Class HV with Class V lupus II nephritis are permitted per cohort. Subjects will be treated with three 28-day cycles of ixazomib or placebo. Subjects who successfully completed 12 weeks of double-blind treatment without any AE resulting in dose modification or discontinuation of the study drug (defined in Section 7.4.3) will be eligible to receive up to 3 additional cycles of open-label ixazomib at the discretion of the investigator and confirmed by the sponsor clinician/designee following the end of the Double-Blind Treatment Period. The subjects need to begin the Open-Label Treatment Extension Period within 4 weeks of completing Cycle 3 of double-blind treatment.

Each 28-day cycle will consist of 3 once-weekly oral doses of 0.5, 2.0, 3.0, or 4.0 mg of ixazomib (dosage strength is stated as the active boronic acid ixazomib) or placebo, depending on the cohort. Subjects who received a dose << 2.0 mg and completed all cycles including the Follow-up Period, will be permitted to re-enroll into the 2.0 and 3.0 mg dose groups, provided they have no drug-related AEs >Grade 1, that required the study drug dose modification, no AEs >Grade 2, continue to meet all inclusion and exclusion criteria, and the SRC (consisting of sponsor personnel and the coordinating investigator) have reviewed and approved

enrollment. Subjects must be receiving standard of care treatment for LN and remain on their current stable and allowed therapies during the screening periodScreening Period and throughout the duration of the study (Section 8.1.1.2).

Subjects can be randomized on Day 1, 24 days after first screening visit (between day -24 and -35) and once safety laboratory tests and inclusion/exclusion criteria have been reviewed and confirmed by the investigator. If the elapsed time between the Screening Visit and Randomization (Day 1) is greater than the allowed screening period, then the eligibility criteria must be re-confirmed in a second screening visit prior to randomization. Disease activity parameters (eg, UPCR, anti-dsDNA, urine sediment and/or complement levels) and safety laboratory tests (hematology and chemistry panel) must be repeated to re-confirm eligibility.

The study consists of the following Periods: a Screening Period (up to 35 days), a **Double-Blind** Treatment Period (Day 1 to Day 84) and **either** a Follow-up Period (Day 85 to Day 168) or an Open-Label Treatment Extension Period (Day 85 to Day 168). For those subjects who enter the Open-Label Treatment Extension Period, visits will be monthly (either for dosing or follow-up) until Day 168, with the last study visit being 30 days after the last open-label dosing or Day 168 whichever is longer. Subjects can be randomized 24 (+11) days after Screening (between Days -24 and -35) and once safety laboratory tests and inclusion/exclusion criteria have been reviewed and confirmed by the investigator. Diagnostic criteria, disease activity measures, and treatment history will be documented, and required laboratory investigations initiated. Subject eligibility will be reviewed by an adjudication committee. The responsibilities and criteria of this committee will be defined in an adjudication charter.

Following verification of eligibility, subjects will return to the clinic on Day 1, undergo baseline assessments, laboratory testing, and will be randomized to either ixazomib or placebo within each cohort/dose level. The **Double-Blind**_Treatment Period eonsistswill consist of three 28-day treatment cycles (Cycles 1, 2, and 3) without intra-subject dose escalation. Subjects will receive ixazomib consisting of drug administrationtreatment on Days 1, 8, and 15 of each 28-day cycle. The second and third eyelecycles will commence on the first day following Day 28 of the preceding cycle (ie, with a period of 13 days between the third drug administration of a cycle and the first drug administration of the following cycle). The treatment period will be limited to 3 complete cycles with ixazomib, with an expected duration of 12 weeks. Double-Blind Treatment Period will be limited to 3 complete cycles with ixazomib or placebo, over an expected duration of 12 weeks. However, the total treatment period may be longer than the standard 12 weeks if delays between cycles are necessary due to AEs. After completion of Cycle 3, the subject will enter the Follow-up Period. A Follow-up Period of up to 3 months, consisting of monthly follow-up visits,3 of the Double-Blind Treatment Period, the subject will either enter the Follow-up Period or enter an optional Open-Label Treatment Extension Period at the investigator's discretion and confirmed by the Takeda

physician/designee. The Follow-up Period or the Open-Label Treatment Extension Period consisting of follow-up visits every 4 weeks will start after the end of the Double-Blind Treatment Period (Day 84) to assess any safety issues. The Open-Label Treatment Extension Period will be limited to up to 3 cycles of treatment with ixazomib on the same dose and schedule that they were receiving in the double blind period over an expected duration of 12 weeks.

Subjects will receive ixazomib cycles consisting of doses of 0.5 mg (Cohort A), 2 mg (Cohort B), 3 mg (Cohort C), andor 4 mg (Cohort D), or placebo. The ascending dose cohorts will be enrolled sequentially. Dosing of subsequent cohorts will not commence until at least 5 subjects in Cohorts A and B and 8 subjects in Cohort C have received at least 1 dose of investigational drug and have reached Day 28 of Cycle 1 or have completed their last evaluation within Cycle 1 with a satisfactory review of all available safety and tolerability data. Subjects discontinued or withdrawn after randomization for nonsafety reasons will only be replaced if the number of subjects per cohort evaluable for safety on Day 28 of Cycle 1 is reduced below 6 subjects for Cohorts C and D, below 5 subjects for lower than 3.0 mg dose cohorts, or the SRC recommends expanding with the same dose to obtain additional information before a dose-escalation decision. Down-titration of ixazomib is permitted for individual subjects for safety and tolerability reasons at any time during the Treatment Period, except for subjects receiving 0.5 mg in Cohort A. If necessary for safety or tolerability reasons or in the judgment of the investigator, ixazomib treatment should be stopped altogether, and an End of Study Visit should be completed. The subject should then complete the remainder of the study period as the Follow-up Period. Dose modification and dose deferral should be discussed with the Sponsor's Medical Monitor; guidelines for the modification or deferral of doses will be provided.

Ixazomib During the Double-Blind Treatment Period, ixazomib will always be dosed at the study site and subjects will return to the clinic for each administration of ixazomib. During the Open-Label Treatment Extension Period, subjects will receive the first dose of each cycle at the clinic and the other 2 weekly doses can be given to the subjects to take at home. All subjects will return to the clinic every 4 weeks to receive the first dose of each cycle. For scheduling flexibility, study visits can occurtake place ± 2 days from each scheduled day during the Treatment Period and ± 1 week during the Follow-Upup Period. A minimum of 120 hours should occur between ixazomib doses. Any variancesvariance in the dosing schedule should not alter the schedule of subsequent dosing.

Subjects will undergo safety laboratory assessments, total **immunoglobulin G, M, and A** (IgG/IgM/IgA), LN assessments including but not limited to UPCR, eGFR anti-dsDNA antibodies, and complement C3 and C4 levels via a central laboratory according to the Scheduleschedule in Appendix A. Pharmacogenomic (PGx) and exploratory biomarker samples will also be sent to a central laboratory for analysis.

Ixazomib is an investigational, orally bioavailable 20S proteasome inhibitor with an estimated $\mathbf{t}_{1/2}$ of ~ 4 to 9 days in plasma. For Cohorts A to D, plasma concentrations of ixazomib over time will be evaluated following the first dose of Cycle 1 and **following** the last dose of Cycle 3.3 of the **Double-Blind Treatment Period**. Predose samples will be collected before each dose in Cycles 1, 2, and 3.3 of the **Double-Blind Treatment Period**. Available PK data will be reviewed as part of the overall safety and tolerability evaluation of ixazomib in LN and for the dose escalation decision.

Recent evidence suggests that genetic variation accounts for differing responses to bortezomib therapy. A single nucleotide polymorphism (SNP) at position 11 in the PSMB1 gene (in the region encoding the leader sequence for the beta subunit of the 20S proteasome) has been associated with reduced proteasome activity and is associated with enhanced bortezomib activity in multiple myeloma and relapsed follicular lymphoma. Company Confidential Information

In addition, hematology and chemistry safety laboratory assessments will be collected before each dose of ixazomib during the Double-Blind Treatment Period and before each cycle of open-label treatment; the results of all available laboratory tests will be reviewed by the Investigatorinvestigator before the administration of the scheduled dose of ixazomib. If the central laboratory results are not available for the Open-Label Treatment Extension Period an additional safety laboratory assessment can be conducted at the local laboratory before dosing and they will be recorded in the electronic case report forms (eCRFs). A negative urine pregnancy testingtest result is required before each administration of investigational drug at the visits specified in the schedule of events table.

In common with other immunosuppressant and cytotoxic agents, ixazomib may have additional effects on host defense. The subject's immunization status should be reviewed at the Screening Visit, and all appropriate vaccinations should be completed at least 1 month before Treatmenttreatment. These may include but are not limited to pneumococcal and inactivated influenza vaccines.

If lymphopenia is noted—after treatment with ixazomib, subjects may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster, and herpes simplex viruses, and cytomegalovirus. Antiviral therapy such as acyclovir or valacyclovir may be initiated at the onset of infection after administration of ixazomib. Other antivirals are also acceptable. Provision of medication will be arranged by the Investigator investigator from local

suppliers and will be reimbursed by the Sponsor.

In oncology studies with ixazomib GI issues, rash and peripheral neuropathy occurred in some subjects. GI effects included diarrhea, nausea and vomiting and to minimize the risk of GI toxicities, subjects with LN should skip dosing with their immunosuppressant drug (eg, MMF) on days of dosing with ixazomib. Peripheral neuropathy will be monitored using the FACT/GOG-NTX neuropathy assessment before the start of each cycle. See Section 10.1.5 for management of AEs of special interest.

Although renal adverse events have been rare in studies with oncology subjects, dehydration due to GI toxicity, concomitant medications and disease progression could contribute to renal dysfunction. Chemistry laboratory parameters including serum creatinine (sCr) will be monitored weekly and treatment discontinued if a decrease >25% in estimated glomerular filtration rate () or doubling in sCr from baseline is observed (see Section 7.4.3).

Each Investigatorinvestigator will review any safety findings and laboratory results to determine if a subject should receive the next dose within each cycle. The investigator will evaluate safety and tolerability for each subject on Day -1 and before each dose during every cycle, as shown in study schematic (Figure 6.a) below. On Day 22 of each cycle during the Double-Blind Treatment Period, the investigator-led team will evaluate all available safety information for the subject to determine eligibility to initiate the subsequent cycle.

Rationale for Change:

At the time of IND submission of this trial the duration of treatment was limited to 3 months by the limited safety data from clinical trial studies (ixazomib was not approved for multiple myeloma) and by the lack of nonclinical toxicology studies. Currently ixazomib, under the trade name Ninlaro, has been approved in more than 40 countries including the EU and US. Over 3000 patients have been exposed to at least 1 dose of either the IV or oral ixazomib formulations across the clinical development program. Some of these patients have received ixazomib for 3 years or more. The emerging safety profile indicates that ixazomib administration can lead to AEs that are generally manageable and reversible with dose reduction and supportive care. In addition the final report for the 6 month (rat) and 9 month (dog) toxicity study reports were submitted to IND 104,482 (SN 0770) on April 1, 2015. In addition the current data from ixazomib cohort 0.5 mg and 2 mg LN dose cohorts demonstrating tolerability of ixazomib in combination with background immunosuppressive, and a PK profile that is similar to what has been observed in oncology patients. Therefore, there are sufficient data to allow an optional open label period with up to 3 cycles of ixazomib at the same dose cohort. The investigator will decide whether their patients may benefit from additional cycles of ixazomib and the sponsor physician must confirm eligibility for each patient to enter open label treatment after reviewing safety data for that patient. The study principal investigators have requested that additional cycles of ixazomib be available as open label treatment for their patients who may benefit as 3 cycles of

ixazomib treatment may not be sufficient for an optimal effect in patients with active LN. The ACR and European guideline also recommend induction therapy for at least 6 months before assessing response and switching treatment. The study is designed to recruit LN patients who have significantly active nephritis and have had inadequate response to current standard of care therapy. The sponsor believes up to 3 cycles open label therapy allows up to 6 months treatment for patients who have been on active drug in the double blind period to assess safety and efficacy of ixazomib for LN induction therapy and will also give an opportunity to patients receiving placebo to have access to active drug treatment. In addition, a physician who is independent from the LN study team will periodically review unblinded clinical data to further safeguard the study participants including those patients who enter to the Open-Label Extension Period.

The following sections also contain this change:

Sections 2.0 STUDY SUMMARY.

- 7.4.3 DLTs, Dose Modifications, and Stopping Rules
- 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling.
- 8.1.2 Storage.
- 8.1.3 Dose and Regimen.
- 9.3.4 Open-Label Treatment Extension
- 13.2 Interim Analysis and Criteria for Early Termination

Appendix A Schedule of Study Procedures: Double-Blind Treatment Period

Change 3: Updated the safety summary conclusion with latest safety data from the Investigator's Brochure.

The primary change occurs in 6.2 Justification for Study Design, Dose and Endpoints

Initial wording:

In conclusion, the safety of ixazomib is supported by clinical experience gained from the ongoing oncology program. As of 27 March 2015, 901 oncology subjects have been treated in unblinded clinical studies with ixazomib as a single agent or in combination with lenalidomide, dexamethasone, melphalan, and/or prednisone, with a median exposure of 4 cycles (range 0 to 76) in patients receiving oral treatment. Additionally, approximately 13% of patients have received more than 12 cycles of oral dosing. Currently, the results from completed, repeat-dose, toxicity studies in rats and dogs of up to seven or ten 28-day cycles with once-weekly dosing support clinical dosing for a total of 10 months in non-oncology indications.

e) Differences in the PK of ixazomib between oncology and LN subjects are expected to be minimal. In terms of demographic parameters the main differences between the 2 populations are age and renal function, which are anticipated to have only a minimal impact on systemic exposure. Participants in this study will be closely monitored, with once-a-week clinic visits during the

Treatment Period and additional clinical assessment / interventions as needed. Overall the risk to LN subjects is expected to be minimal.

Amended or new wording:

In conclusion, the safety of ixazomib is supported by clinical experience gained from the ongoing oncology program. As of 27 March 2015, 901 oncology subjects have been treated in unblinded clinical studies with ixazomib as a single agent or in combination with lenalidomide, dexamethasone, melphalan, and/or prednisone, with a median exposure of 4 cycles (range 0 to 76) in patients receiving oral treatment. Additionally, approximately 13% of patients have received more than 12 cycles of oral dosing. Currently, the results from completed, repeat-dose, toxicity studies in rats and dogs of up to seven or ten 28-day cycles with once-weekly dosing support elinical dosing for a total of 10 months in non-oncology indications 2017, data are available from 941 patients known to have received at least 1 dose of either the IV or oral ixazomib formulations across the oncology clinical development program; in addition, 2682 patients have been enrolled in phase 3 clinical studies in RRMM, newly diagnosed MM and RRAL. The emerging safety profile indicates that ixazomib administration can lead to AEs that are generally manageable and reversible with dose reduction and supportive care. Additionally, the AEs in the combination studies are consistent with the safety profile of the individual agents in the combination regimen (eg, myelosuppression is common in regimens containing melphalan, and rash is common in regimens containing lenalidomide). While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention.

f) Differences in the PK of ixazomib between oncology and LN subjects are expected to be minimal. In terms of demographic parameters the main differences between the 2 populations are age and renal function, which are anticipated to have only a minimal impact on systemic exposure. Participants in this study will be closely monitored, with once-a-week clinic visits during the Double-Blind Treatment_Period, at least monthly visits at the Open-Label Treatment Extension Period and additional clinical assessment / interventions as needed. Overall the risk to LN subjects is expected to be minimal.

Rationale for Change:

To update safety data from the latest IB.

Change 4: Revised Inclusion Criterion 5 to allow subjects who have proteinuria ≥1 g/day due to a recent lupus nephritis (LN) flare, and who are refractory to current standard of care for those subjects who do not have a kidney biopsy within 2 years of the Screening.

The primary change occurs in 7.1 Inclusion Criteria

Initial wording:

- 5) The subject has a definite diagnosis of LN based on a kidney biopsy done within 2 years of the Screening Visit which demonstrated ISN/RPS class III, IV or V changes [excluding Class III (C), IV-S (C) and IV-G (C)] or WHO 1982 classification Class III, IV or V (excluding Class IIIc and IVd) (see Appendix I).
 - a) If no biopsy was done within 2 years of Screening Visit, biopsy can be done during the screening period as a study procedure.
 - b) Co-existence of classes is permitted.

Amended or new wording:

- 5. The subject has a definite diagnosis of LN based on a kidney biopsy done within 2 years of the Screening Visit which demonstrated ISN/RPS elass III, IV or V changes [excluding Class III (C), IV-S (C) and IV-G (C)] or WHO 1982 classification Class III, IV or V (excluding Class IIIc and IVd)(see Appendix I).
 - a) If no biopsy was done within 2 years of Screening Visit, biopsy can be done during the screening period as a study procedure.
 - b) Co-existence of classes is permitted.
 - c) Subjects with a confirmed diagnosis of LN who have not had a renal biopsy within 2 years of screening and cannot have a renal biopsy during the screening, may be eligible for the study if they have proteinuria of ≥1 g/24 hours due to a LN renal flare occurring within 1 year of the screening. A LN renal flare is defined as at least a doubling of proteinuria with no other explanation such as a secondary pathology (eg, diabetic nephropathy) or change in medication (eg, reduction of angiotensin-converting enzyme/angiotensin II receptor blocker).

Rationale for Change:

In current clinical practice a significant number of LN patients are treated with standard of care therapy (high dose corticosteroids and immunosuppressives) without performing a renal biopsy. The ACR or the European League Against Rheumatism guidelines provide recommendations to change in immunosuppressive therapy if a patient does not adequately respond to 6 months of induction therapy [1]. However the guidelines do not provide recommendations when to repeat or perform an initial biopsy or change therapy based on failure of current treatment. Recruiting patients who have a significant proteinuria (≥1 g/24 hour) due to LN flare within 1 year of study entry and refractory to the current standard of care, will not change the primary objectives of this study, which are safety, tolerability, PK characterization, and evaluation of a signal of efficacy by assessing a change in proteinuria (UPCR) and SLE autoantibody (eg, anti-dsDNA and serum complements). The exclusion of patients with an eGFR of <30 mL/min/1.73 m² will decrease the

likelihood that the proteinuria is primarily due to chronic GN. In addition, it is unlikely that Class I or II patients will qualify based on this criterion as the patients in this trial are required to be receiving maintenance therapy with either mycophenolate or azathioprine, which are effective treatments for these classes of LN. Therefore, LN patients who had a recent renal flare and are refractory to the current SOC can be recruited without requiring a renal biopsy within 2 years of the screening, which will not affect the objectives of the study and may allow a larger proportion of patients with GN to potentially benefit from ixazomib.

Change 5: Revised Inclusion Criterion 6 to allow subjects with Class V or Class V with Class II nephritis and urine protein creatinine ratio levels of ≥ 1 into the study rather than current criteria of ≥ 3 .

The primary change occurs in 7.1 Inclusion Criteria

Initial wording:

- 6. The subject has a renal biopsy demonstrating either ISN/RPS or WHO class V or class V with class 2 nephritis with a UPCR of >3 or the subject has a renal biopsy demonstrating either active ISN/RPS or WHO class III or IV nephritis, defined by either one of the following criteria:
 - a) A UPCR* of ≥1.0 at Screening

OR

- i. A UPCR* > 0.5 at Screening and at least one of the following:
- i. Active urine sediment in the absence of infection or other cause within 3 months of screening, defined as at least one of the following:
 - ≥5 red blood cells (RBC) per high power field, not due to causes other than lupus nephritis.
 - \geq 5 white blood cells (WBC) per high power field in the absence of infection.
 - Presence of cellular casts.
- ii. The subject has increased levels (above upper limit of normal [ULN] serum dsDNA autoantibodies at screening.
- iii. Low complement (either C3 or C4) at Screening ($\geq 25\%$ lower than LLN).
- iv. Biopsy within 3 months prior to screening visit indicating active proliferative lupus glomerulonephritis ISN/RPS class III or IV changes [excluding Class III (C), IV-S (C) and IV-G (C)] or WHO 1982 classification Class III or IV (excluding Class IIIc and IVd), with co-existing Class V permitted.
 - *Subjects may be re-screened once for urinary sediment, proteinuria or complement levels within 2 weeks of the original screening visit.
 - * UPCR value for eligibility will be based on the average UPCR obtained

from the 3 specimens collected during screening.

Amended or new wording:

The subject has a renal biopsy demonstrating either ISN/RPS or WHO elassClass V or elassClass V with elassClass 2 nephritis with a UPCR of ≥3≥1 or the subject has a renal biopsy demonstrating either active ISN/RPS or WHO elassClass III or IV nephritis, defined by either one of the following criteria:

a) A UPCR* of ≥1.0 at Screening

OR

- b) A UPCR* >0.5 at Screening and at least one of the following:
 - i. Active urine sediment in the absence of infection or other cause within 3 months of screening, defined as at least one of the following:
 - \geq 5 red blood cells (RBC) per high power field, not due to causes other than LN.
 - \geq 5 white blood cells (WBC) per high power field in the absence of infection
 - Presence of cellular casts.
 - ii. The subject has increased levels (above upper limit of normal [ULN] serum dsDNA autoantibodies at screening.
 - iii. Low complement (either C3 or C4) at Screening (≥25% lower than the lower limit of normal [LLN]).
 - iv. Biopsy within 3 months before screening visit indicating active proliferative lupus glomerulonephritis ISN/RPS class III or IV changes [excluding Class III (C), IV-S (C) and IV-G (C)] or WHO 1982 classification Class III or IV (excluding Class IIIc and IVd), with coexisting Class V permitted.
 - *Subjects may be re-screened once for urinary sediment, proteinuria or complement levels within 2 weeks of the original screening visit.
 - g) * UPCR value for eligibility will be based on the average UPCR obtained from the 3 specimens collected during screening.

Rationale for Change:

In this amendment, the sponsor has modified the inclusion criteria to allow inclusion of LN subjects with class V LN if they have UPCR ≥1. The primary objective of this trial is to characterize the safety and tolerability of ixazomib in the LN population and to evaluate if there is an efficacy signal. Proteinuria of 1 g/24 hr or greater is considered as indicative of clinically active disease and suitable for enrolment into a 12 week study as this group of patients has been refractory to standard of care therapy with immunosuppressive drugs and/or corticosteroids. Reducing proteinuria to less than 500 mg/day in patients with proteinuria of one or greater, may

have a long term beneficial effect on the disease prognosis. The sponsor proposes that reducing threshold of proteinuria in Class V LN from UPCR >3 to UPCR of ≥1 will not affect significantly the study primary objectives, which are safety, tolerability, PK characterization, and evaluation of a signal of efficacy and may allow a larger proportion of patients with LN who may benefit from ixazomib to enter into the trial.

Change 6: Revised Inclusion Criterion 11 to allow subjects who received ≤2.0 mg ixazomib in earlier cohorts, rather than <2 mg ixazomib, to be re-enrolled into Cohorts B and C (2.0 mg and 3.0 mg).

The primary change occurs in 7.1 Inclusion Criteria

Initial wording:

- 11. This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized) and subjects who received a dose <2.0 mg and have completed all cycles including the Follow-up Period. If re-enrolled, the subject must be re-consented.
 - * The re-enrollment of all subjects who received a dose <2.0 mg and completed all cycles including the Follow-up Period is permitted to Cohort B or C (2.0 mg and 3.0 mg dose cohorts) after completion of all cycles including the follow-up period if they had no drug-related AEs greater than Grade 1, no AEs greater than Grade 2, continue to meet all inclusion and exclusion criteria, and the SRC has reviewed and approved enrollment of the subject into a higher dose cohort.

Amended or new wording:

- 11. This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized) and subjects who received a dose <<2.0 mg and have completed all cycles including the Follow-up Period. If re-enrolled, the subject must be re-consented.
 - * The re-enrollment of all subjects who received a dose <<2.0 mg and completed all cycles including the Follow-up Period is permitted to Cohort B orand C (2.0 mg and 3.0 mg dose cohorts) after completion of all cycles including the follow-up period if they had no drug-related AEs greater than Grade 1 which required study drug dose modification, no AEs greater than Grade 2, continue to meet all inclusion and exclusion criteria, and the SRC has reviewed and approved enrollment of the subject into a higher dose cohort.

Rationale for Change:

In the amendment, it is proposed that subjects in the 2 low dose cohorts (0.5 mg and 2.0 mg dose cohorts) are allowed to enrol in the 2.0 mg and 3.0 mg cohorts if they meet the inclusion criteria of the protocol and: 1) they have completed the 6-month study period at the 0.5 mg or 2.0 mg dose, 2) they continue to meet inclusion and exclusion criteria, 3) they have not had drug-related AEs >Grade 1, 4) they have not had any AE >Grade 2, and 5) they are approved to re-enrol by the study safety reveiw committee. Due to the proposed study design, there is expected to be no additional risk for subjects to re-enroll into a higher dose cohort. As subjects entering the trial

have evidence of active renal disease, the sponsor believes they should be allowed to be randomized into the higher dose cohort to increase their chance of receiving benefit from study at dose levels closer to those shown to be effective in oncology patients. As a result, following investigators' request, this amendment addresses investigators' concerns by allowing patients with active LN refractory to the current standard of care to re-enroll to the 3 mg dose cohort from the lower dose cohorts for potential improved efficacy.

Based on the plasma half-life of ixazomib (approximately 9 days), accumulation of ixazomib in plasma is anticipated to be minimal following completion of study treatment in the 0.5 mg and 2.0 mg dose cohorts and the associated 3 month follow up period. The follow-up within this study following the end of treatment (Day 84) is 3 months (Day 168), total washout of ixazomib of approximately 9 times longer than the terminal half-life. Overall no additional risk is expected to be for subjects to re-enroll into a higher dose cohort.

The following sections also contain this change:

- **2.0** STUDY SUMMARY
- **6.1** Study Design
- **6.2** Justification for Study Design, Dose and Endpoints

Change 7: Revised Exclusion Criterion 10 to add a stipulation to IgG <75% of lower limit of normal to allow subjects with IgG >4.2 g/dL into the study if the cause of low IgG is due to LN proteinuria and all other causes of hypo-gammaglobulinemia have been ruled out

The primary change occurs in 7.2 Exclusion Criteria

Initial

10. The subject has one of the following laboratory test values:

wording:

a) IgG <75% of LLN.

Amended or new wording:

10. The subject has one of the following laboratory test values:

a) IgG <75% of LLN. If low IgG is due to significant proteinuria due to LN activity, subjects with IgG >4.2 g/dL can be included. The cause of low IgG must be due to LN proteinuria and all other causes of hypogammaglobulinemia must be ruled out.

Rationale for Change:

At the time of IND submission of this trial, ixazomib was not approved for multiple myeloma and there were limited safety data available. As a result the current protocol excluded subjects with IgG <75% of the normal limit which exclude a significant number of LN patients with severe proteinuria because they will also lose immunoglobulin through proteinuria. Hypogammaglobulinemia will be improved in these patients only if the disease activity is treated. Hypogammaglobulinemia has not been a common side effect in oncology patients including those who have received ixazomib for a few years. Therefore, the inclusion criterion has been modified to decrease the threshold of IgG at screening to >4.2 g/dl, if due to LN

proteinuria and other causes of low IgG and immunodeficiency have been ruled out. Additionally, the patient must not have had a moderate/severe infection in the last 6 months before screening. In addition, the current protocol stopping criteria are maintained; if the IgG level declines to less than 50% of the LLN, dosing of ixazomib must stop. This modification will allow more patients with more severe proteinuria due to LN and who are refractory to current SOC to potentially benefit from ixazomib treatment.

Amendment 11 to A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Multiple Rising Doses of MLN9708 for the Treatment of Subjects With ISN/RPS Class III or IV Lupus Nephritis

ELECTRONIC SIGNATURES

Signed	by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personal Protected Data	Statis	tical Approval	04-Dec-2017 19:10 UTC
	Clini	cal Pharmacology Approval	04-Dec-2017 22:56 UTC
	Clini	cal Science Approval	05-Dec-2017 17:15 UTC